Use of models in study design for dynamic systems: Ebola vaccine trial design

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DAIDD
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White Oak Conservation

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The ICI3D Figshare Collection

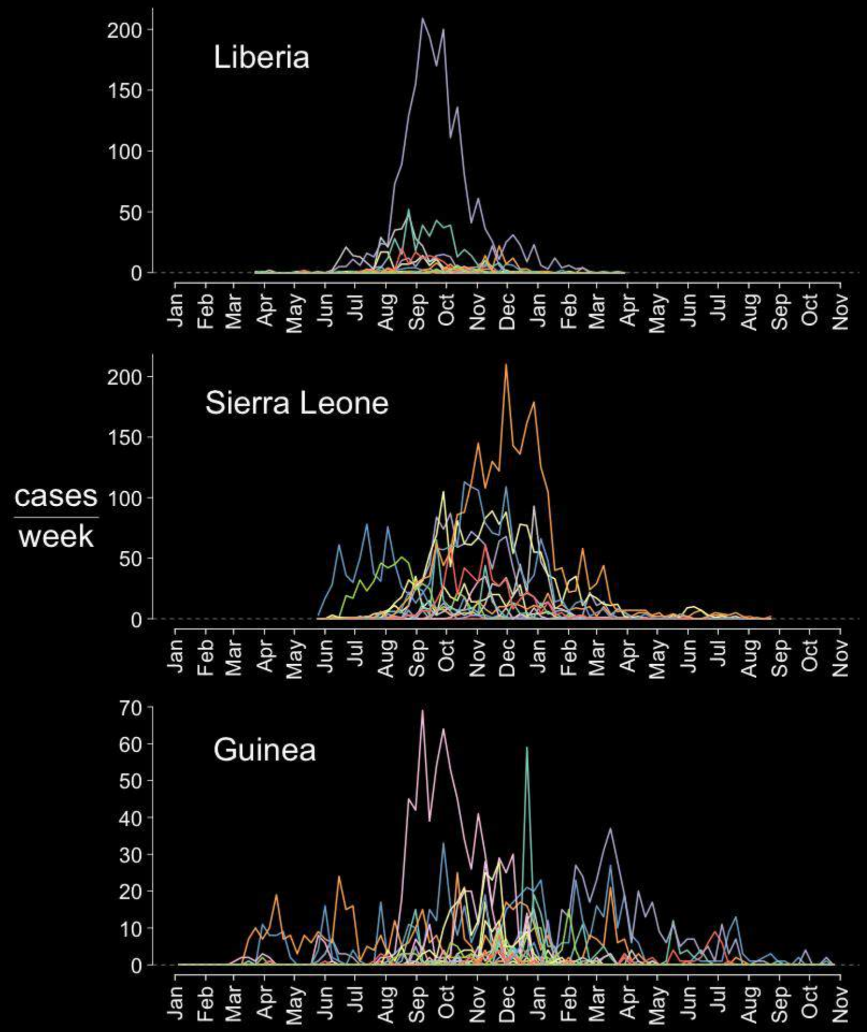
Goals

- Understand data-centric and process-centric perspectives.

- Learn how simulation can guide trial design

The West African Ebola Epidemic

- What processes drive the epidemic?
- Who is at highest risk?
- When will it peak/end?
- Which interventions work?
- Optimal allocation of sparse resources?



Infectious Disease Research

Logistical, financial and ethical constraints limit quantity & quality of data

Perspectives from Two Disciplines

Classical Epidemiology	Mechanistic Epidemiology
Data-Centric	Process-Centric
(Public Health)	(Disease Ecology)
Risk Factors	Infectious Disease Dynamics
Biostatistics	Mathematical Modeling

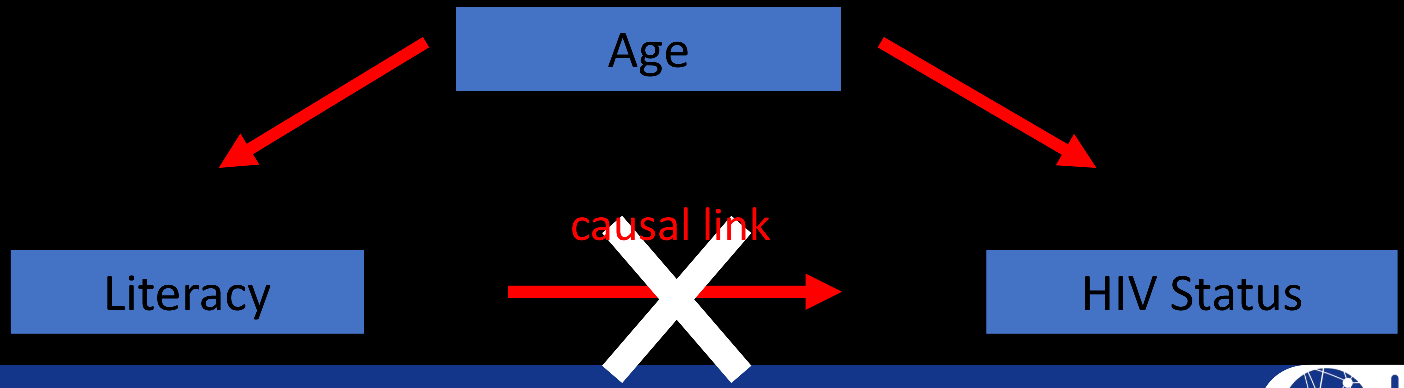
Classical Epidemiology

- Does A cause B?

Classical Epidemiology

Individual	Literate	HIV infected
1	0	0
2	0	0
3	0	0
4	0	1
5	1	1
6	1	0
7	1	1
8	1	1

- Does literacy cause HIV?
- Find correlations that imply causality by accounting for
  1. random error: do we have enough data?
  2. bias: are design & analysis valid?



Classical Epidemiology

Infer causation via carefully identified correlations

Minimize bias via:

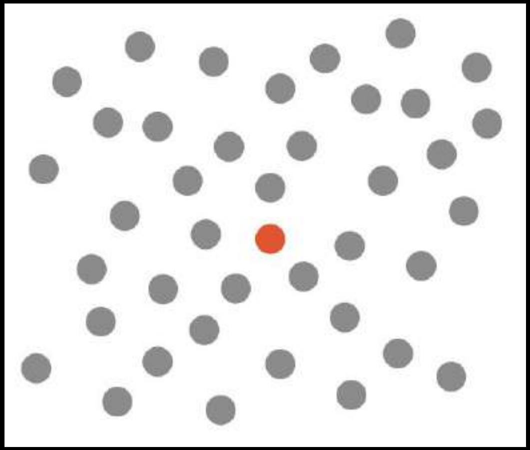
- study design: e.g. randomization, blinding
- analytical methods: e.g. causal inference modeling

What do *Introductory Epidemiology* courses teach?

- Measures of Disease
- Measures of Effect (of a risk factor)
- Study Designs for Measuring Effects
  - Dealing with random error
  - Dealing with confounding
  - Dealing with bias
- Biostatistical analyses for analyzing data

Mechanistic Epidemiology

- Scale up from individual processes to population patterns



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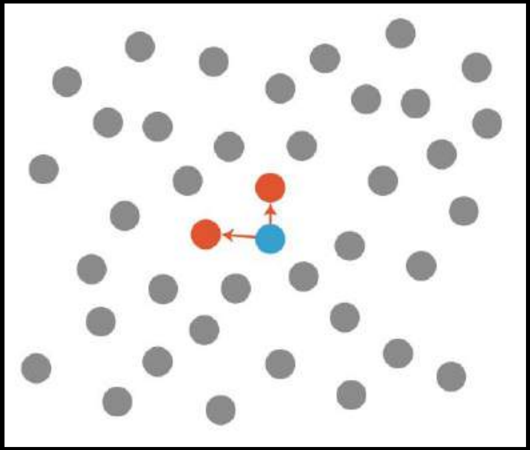

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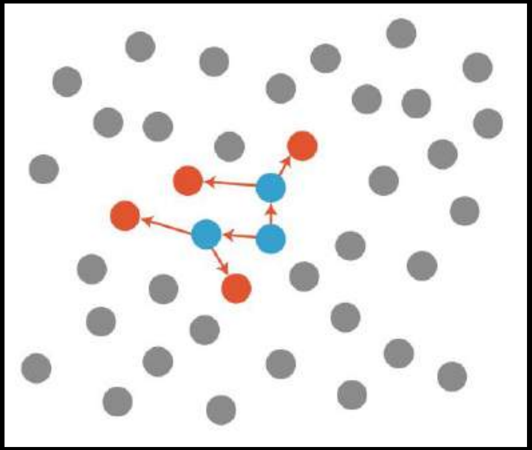

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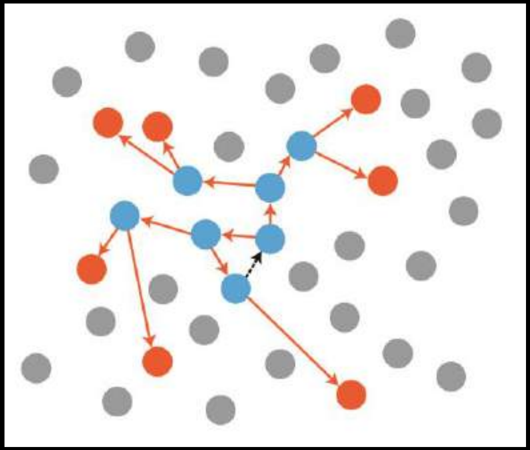

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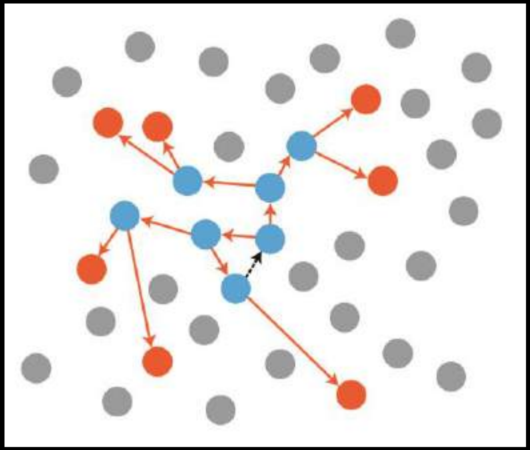
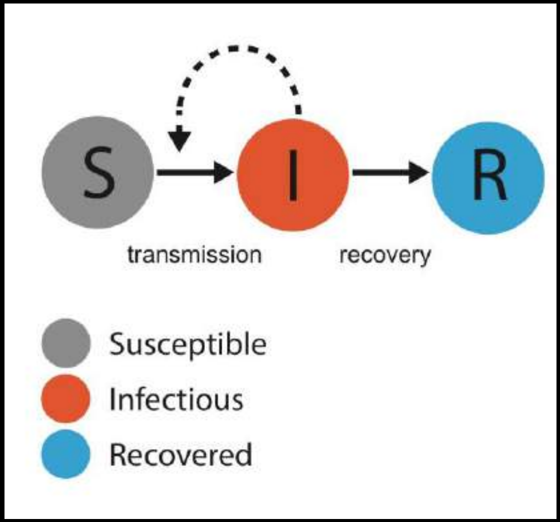


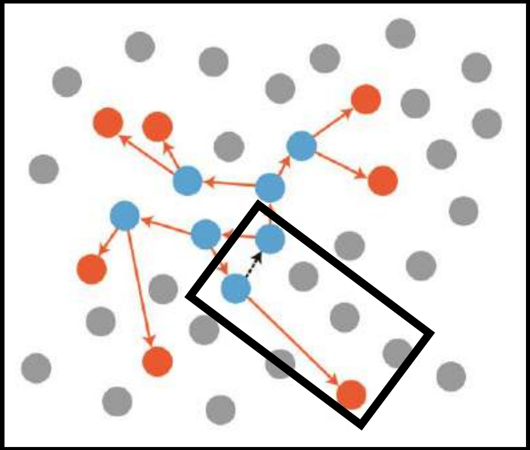
solid arrow = flow between disease states
dashed arrow = influence



How do contact processes cause epidemics?

Mechanistic Epidemiology

- Scale up from individual processes to population patterns



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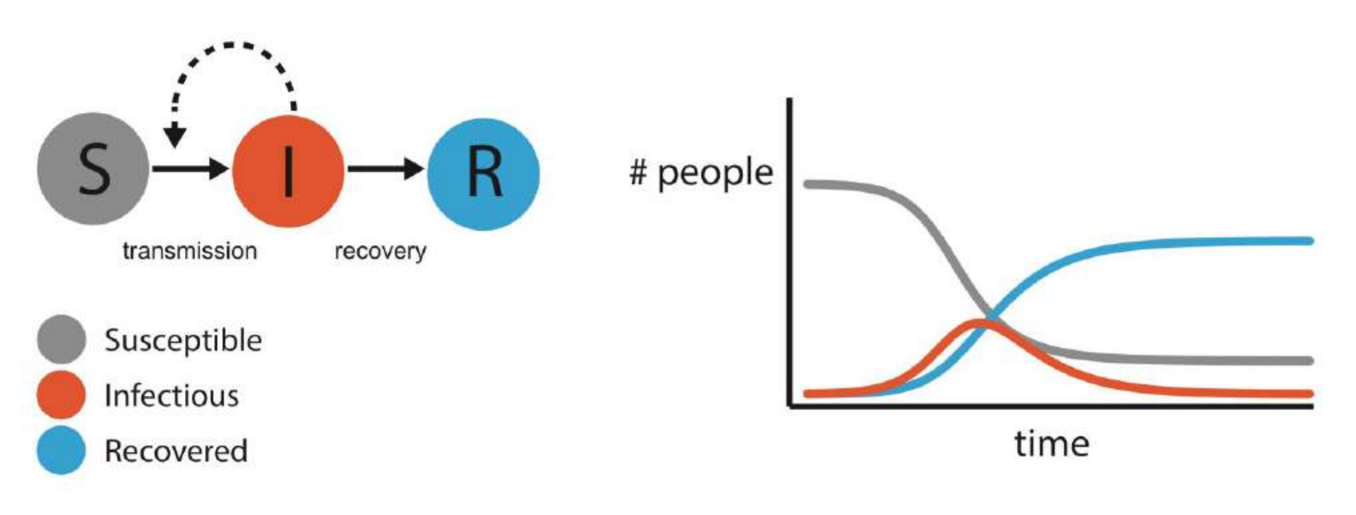
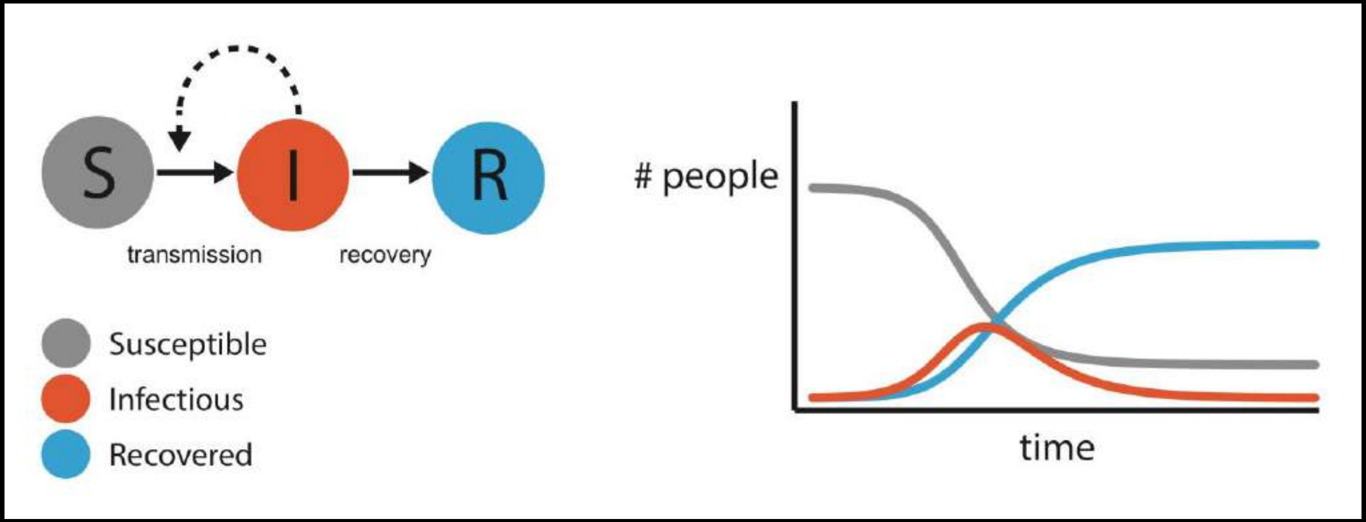


Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- "What if" scenarios not amenable to experimentation



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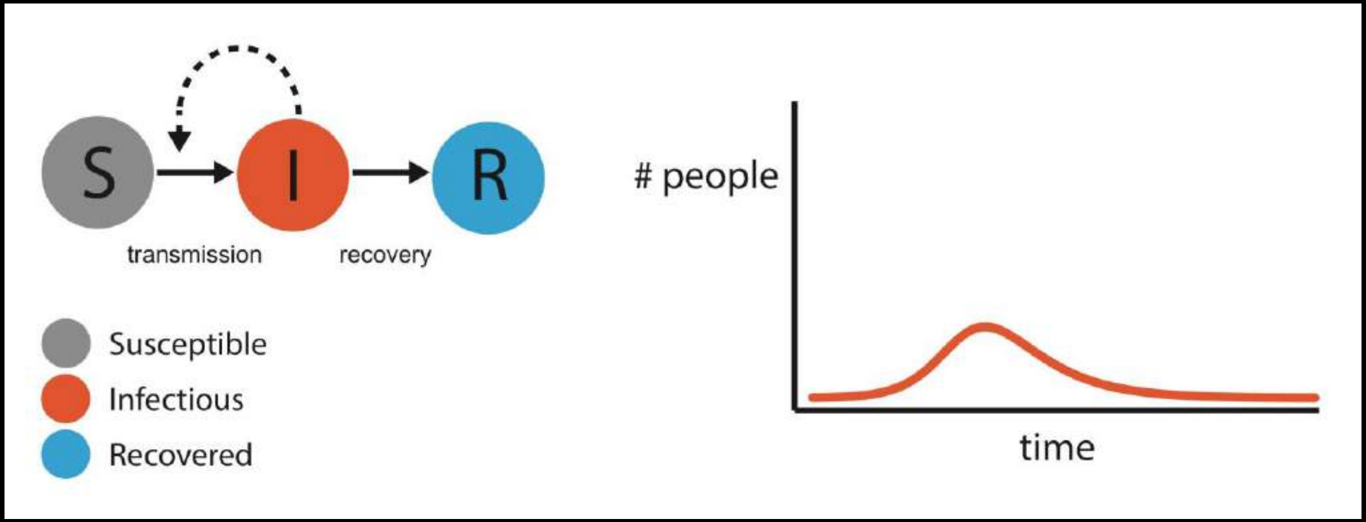

Mechanistic Epidemiology

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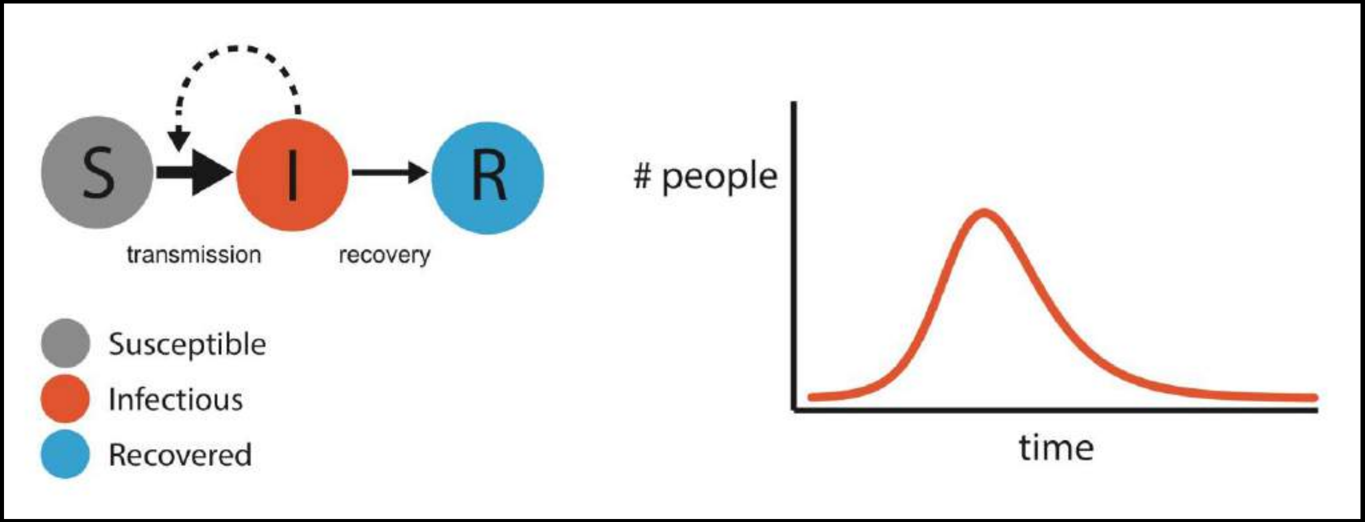
- “What if” scenarios not amenable to experimentation

What if each person exposed 50% more people?



Mechanistic Epidemiology

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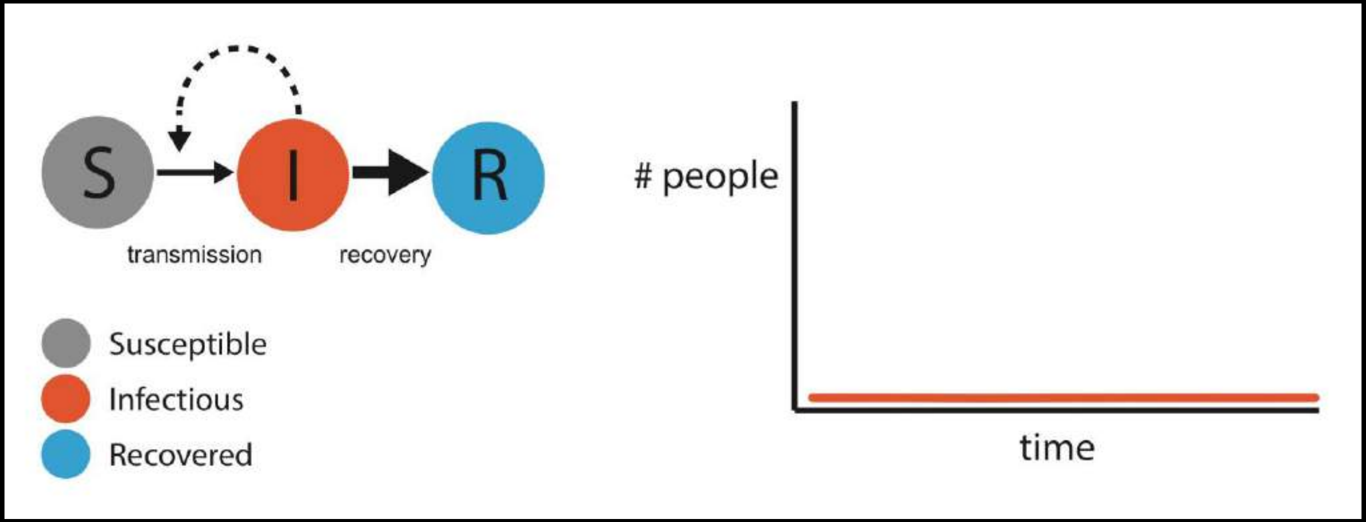
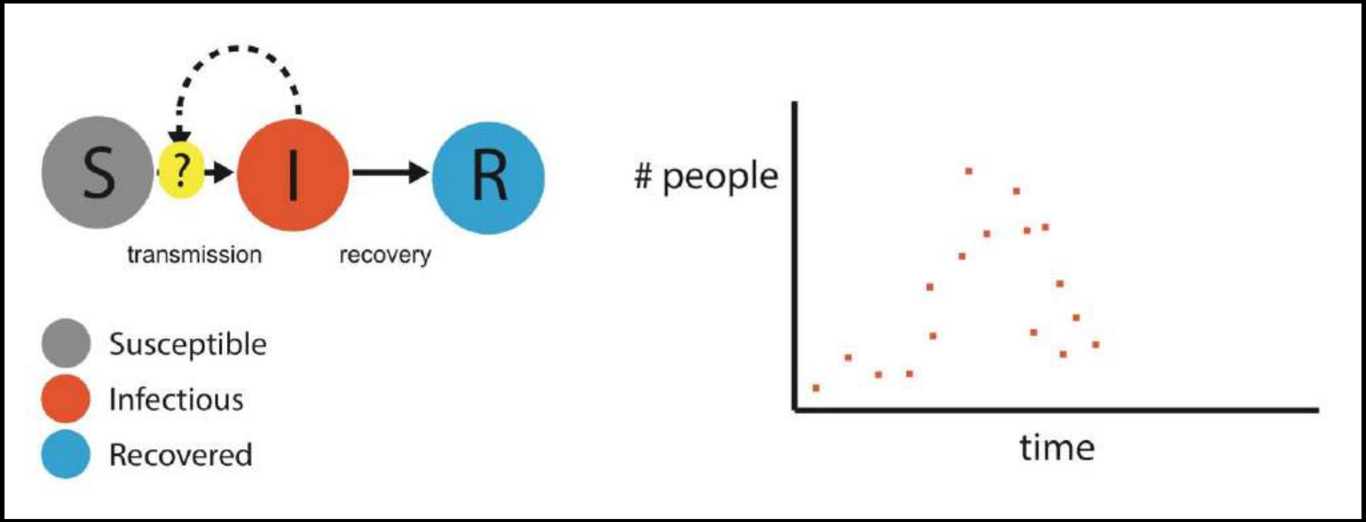
- “What if” scenarios not amenable to experimentation

What if we treated people and doubled the rate of recovery?



Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- “What if” scenarios not amenable to experimentation
- Estimating parameters by fitting available data



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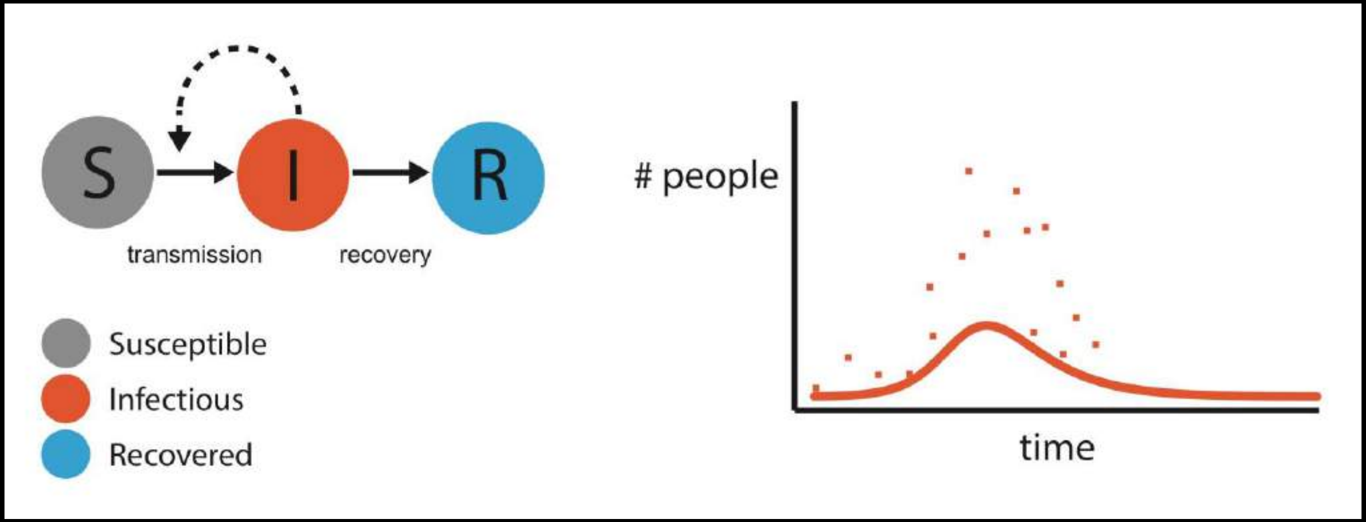

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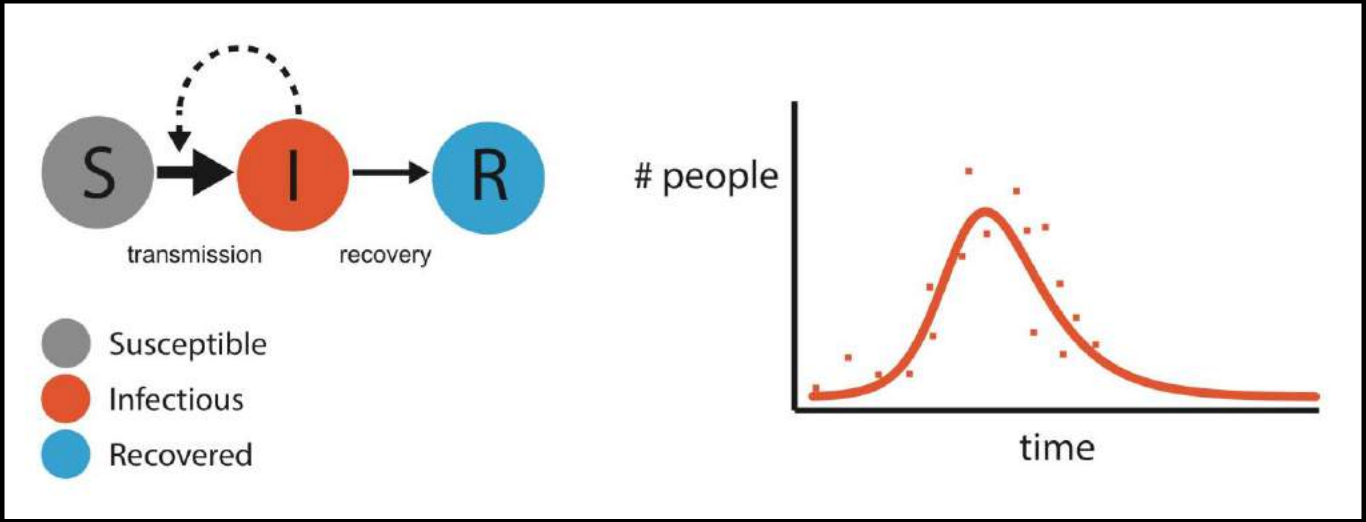

Mechanistic Epidemiology

- Scale up from individual processes to population patterns
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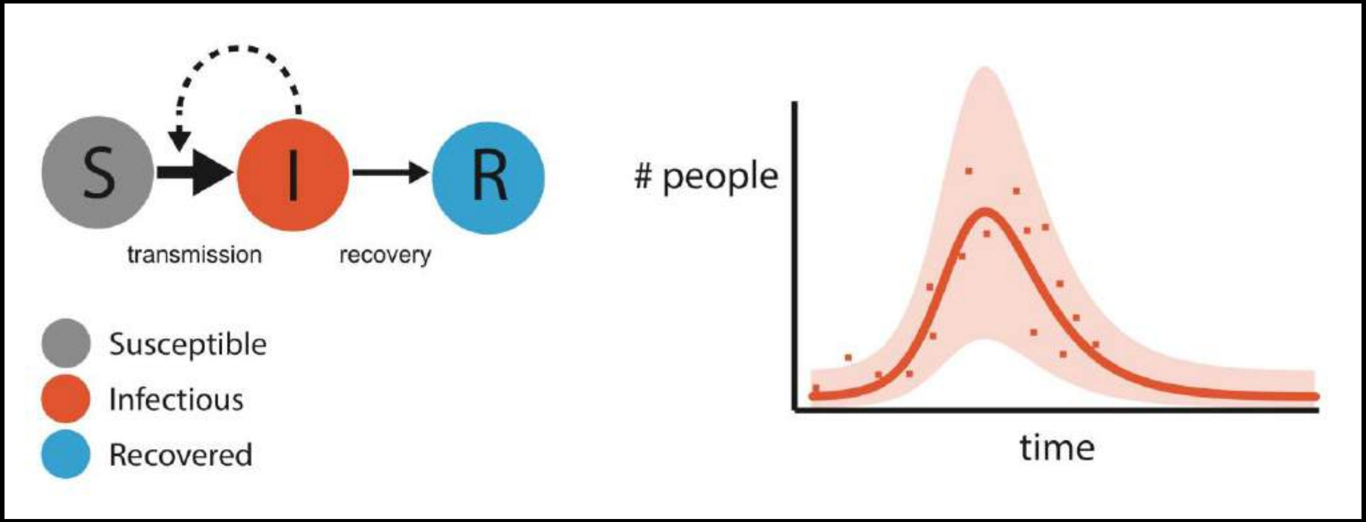
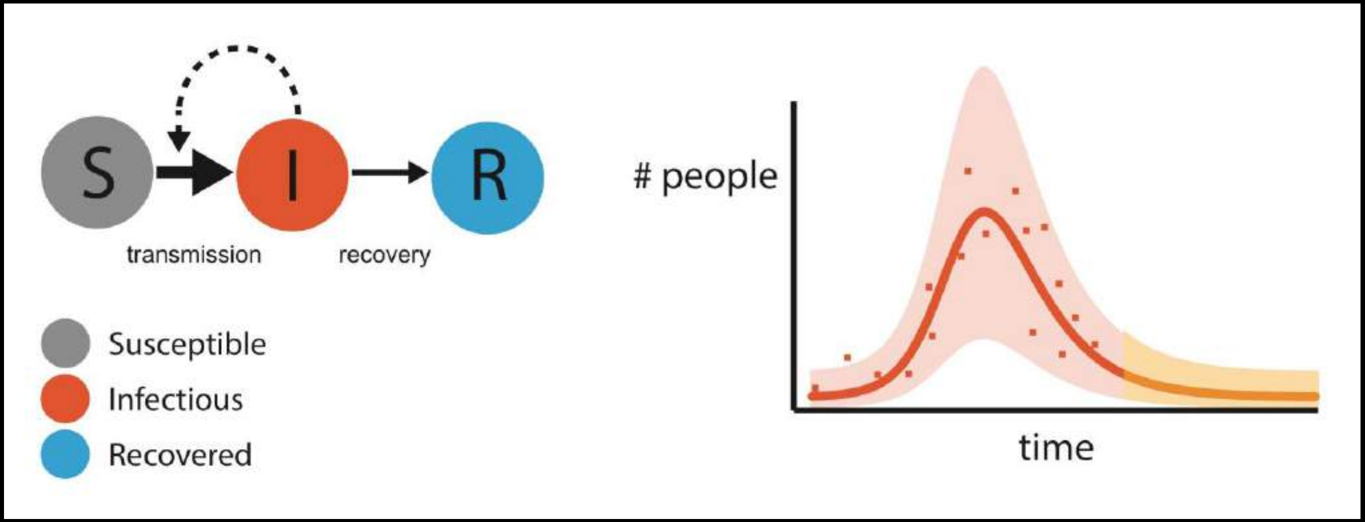
- Estimating parameters by fitting available data

Estimate transmission rate or other model parameters
(with confidence intervals)



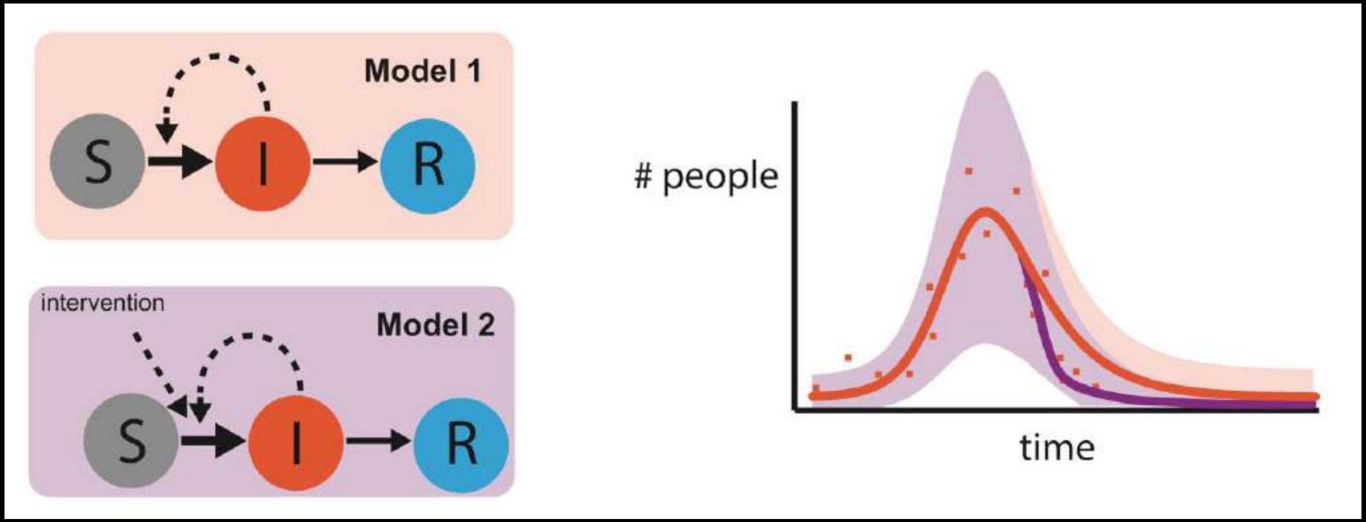
Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- "What if" scenarios not amenable to experimentation
- Estimating parameters by fitting available data
- Prediction



Mechanistic Epidemiology

- Scale up from individual processes to population patterns
- “What if” scenarios not amenable to experimentation
- Estimating parameters by fitting available data
- Prediction
- Model selection (choosing between alternative hypotheses)



Mechanistic Epidemiology

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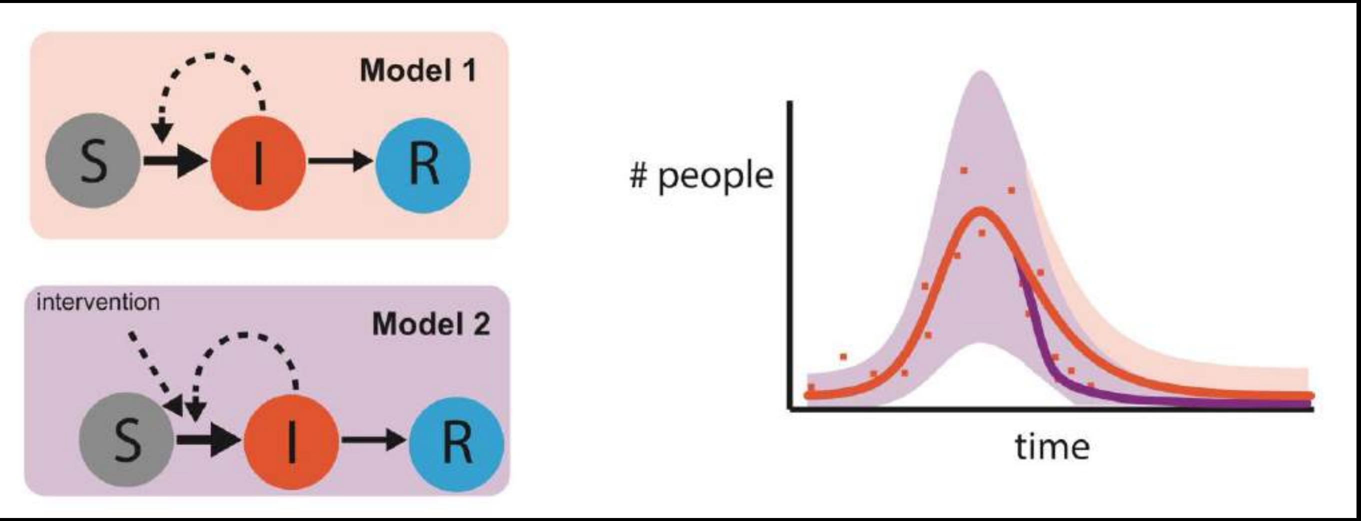
- Estimating parameters by fitting available data
- Prediction
- Model selection

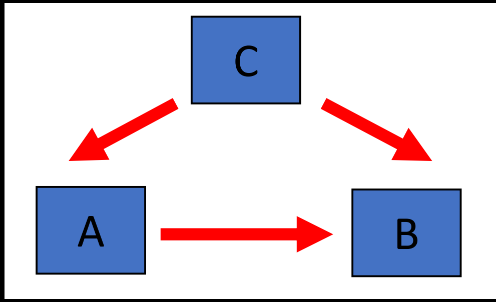
data focus emerged in last 10 years



Classical Epidemiology

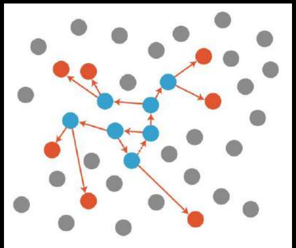
Data-Centric

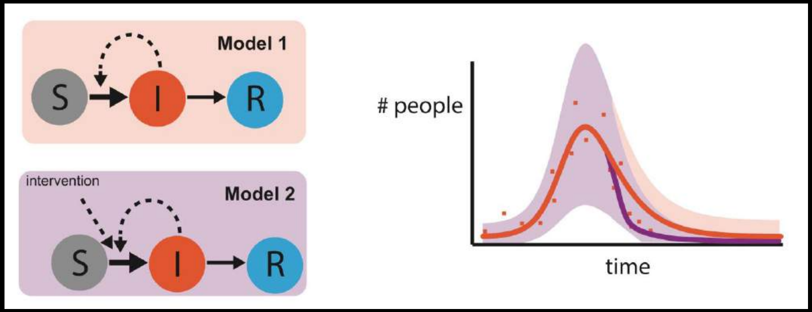
Individual	Literate	HIV infected	Age	SES
1	0	0	5	high
2	0	0	8	high
3	0	0	7	low
4	0	1	16	low
5	1	1	35	low
6	1	0	28	high
7	1	1	18	low
8	1	1	45	high



Mechanistic Epidemiology

Process-Centric





An Integrative Approach

Mechanistically model both <u>observation processes</u> & underlying <u>epidemiological processes</u>

Vaccine Efficacy Trials

- Compare disease risk between *vaccinated* & *unvaccinated* participants.
- If high risk people choose to be vaccinated, confounding
- Confounding avoided by randomization
- Randomized double-blinded placebo-controlled trials

Is randomization ethical?

<u>Equipoise</u>

Uncertainty regarding whether
a participant is better off
receiving intervention or placebo.

Stepped Wedge Cluster Trial

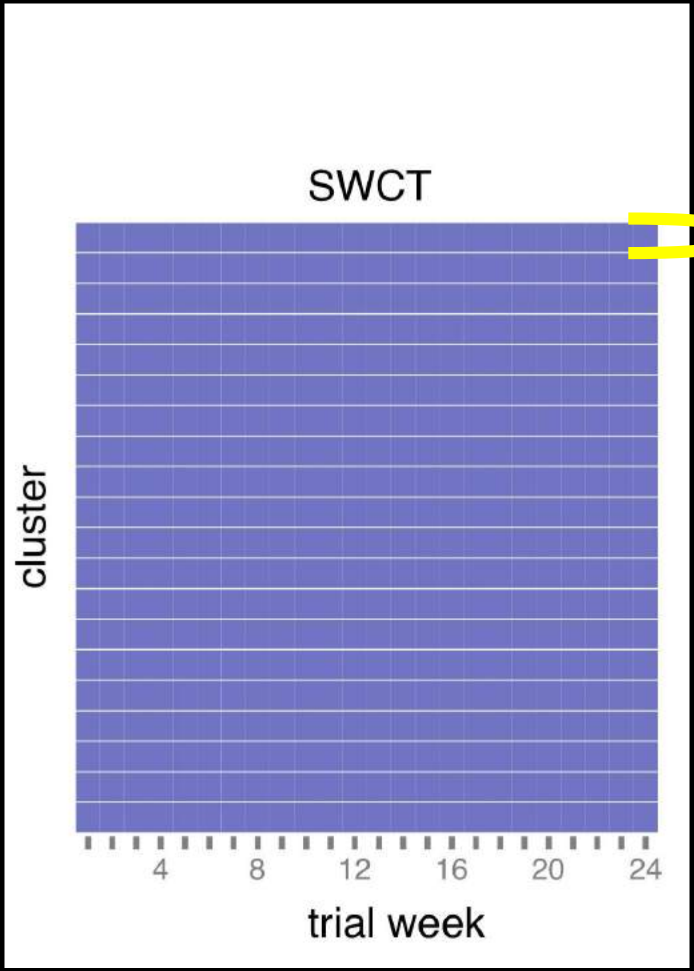
- Evaluate vaccine when ethically problematic to withhold intervention

- Vaccinate everyone *as fast as possible*, by groups, in random group-order

- Compare infection risk between *vaccinated* & *not-yet-vaccinated* individuals

- Randomized group-order avoids confounding

Stepped Wedge Cluster Trial

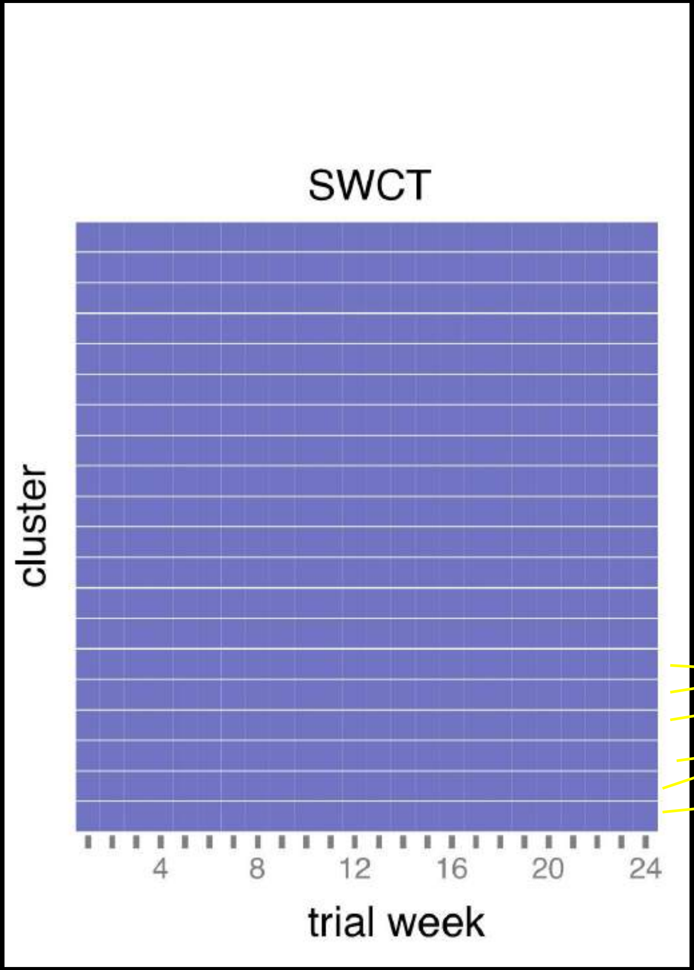


Cluster of 300 frontline caregivers (HCW+)

x20

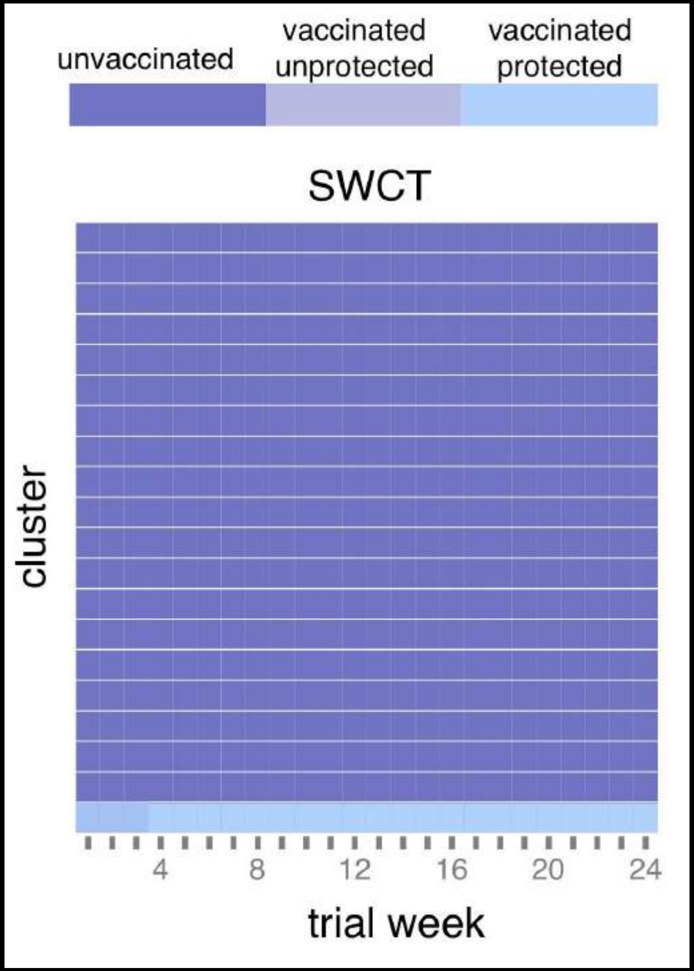
Observed for 24 weeks (6 months)

Stepped Wedge Cluster Trial



Clusters from geographically distinct areas

Stepped Wedge Cluster Trial



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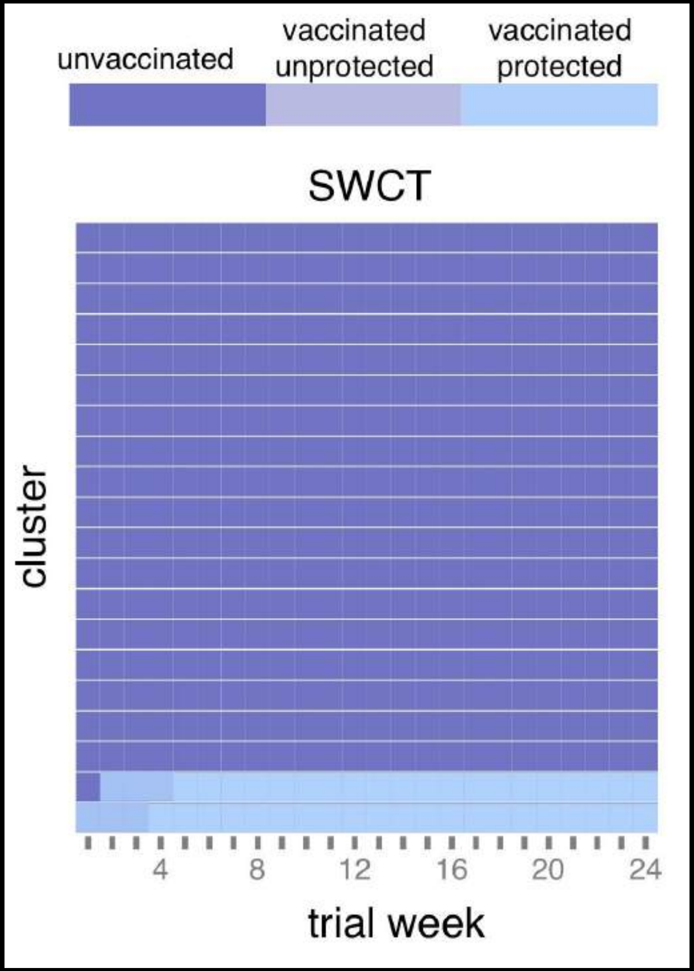

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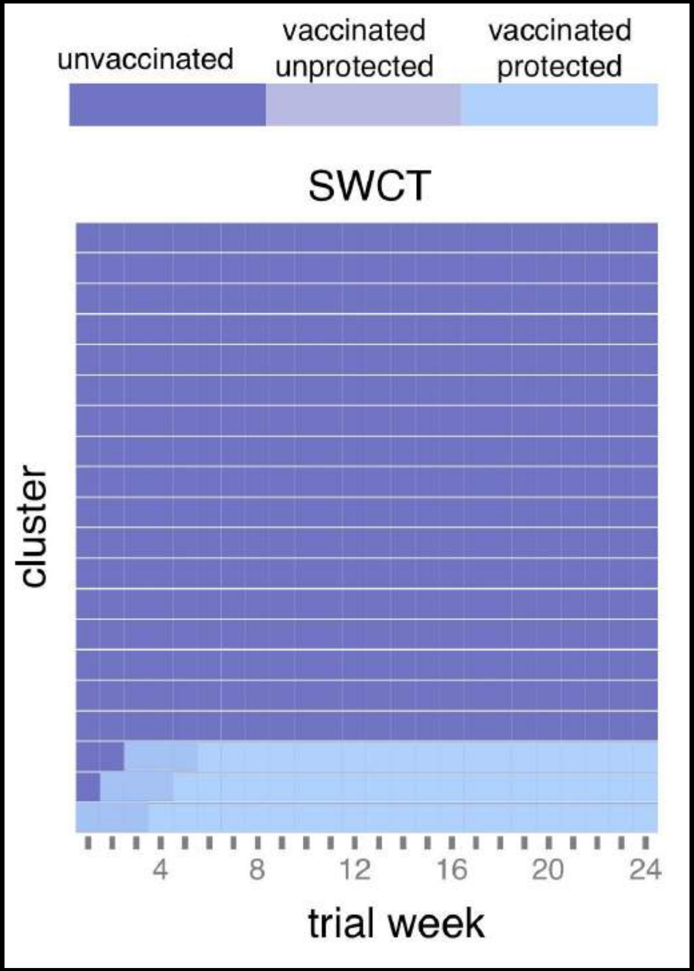

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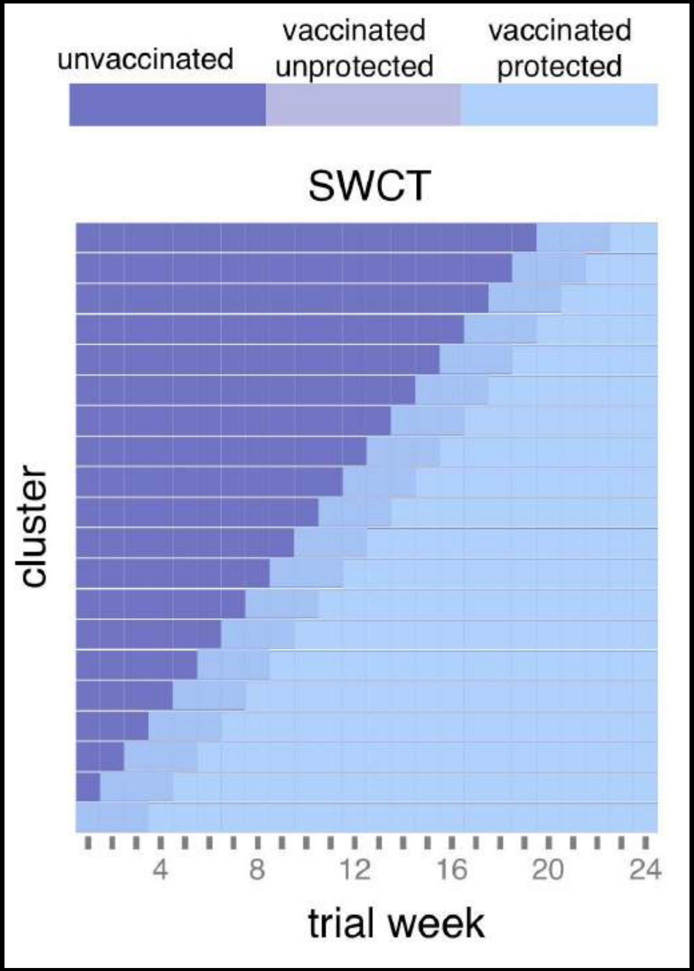

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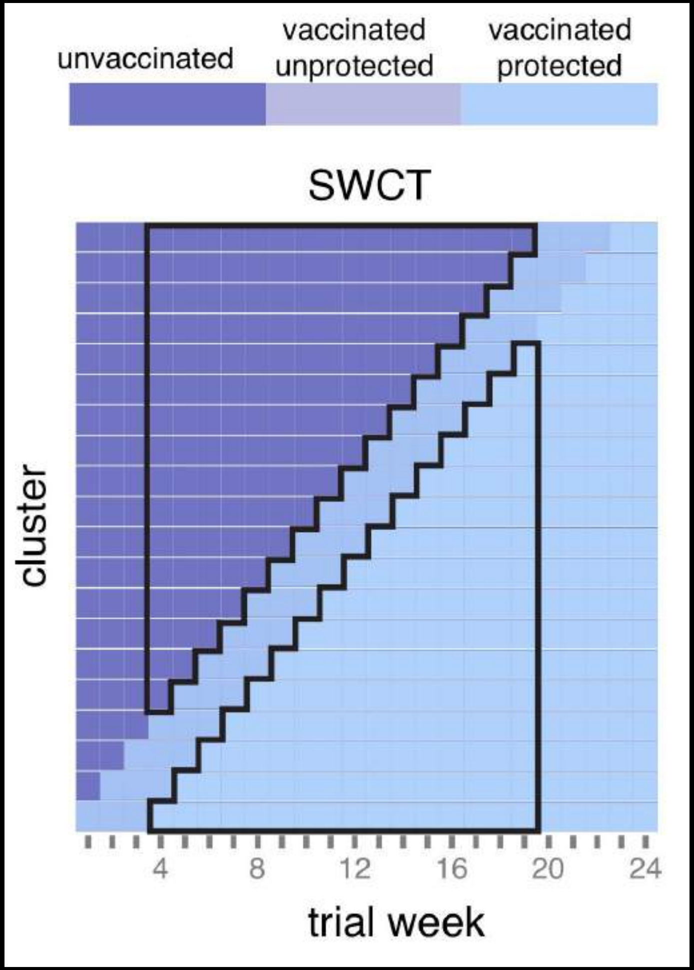
Stepped Wedge Cluster Trial



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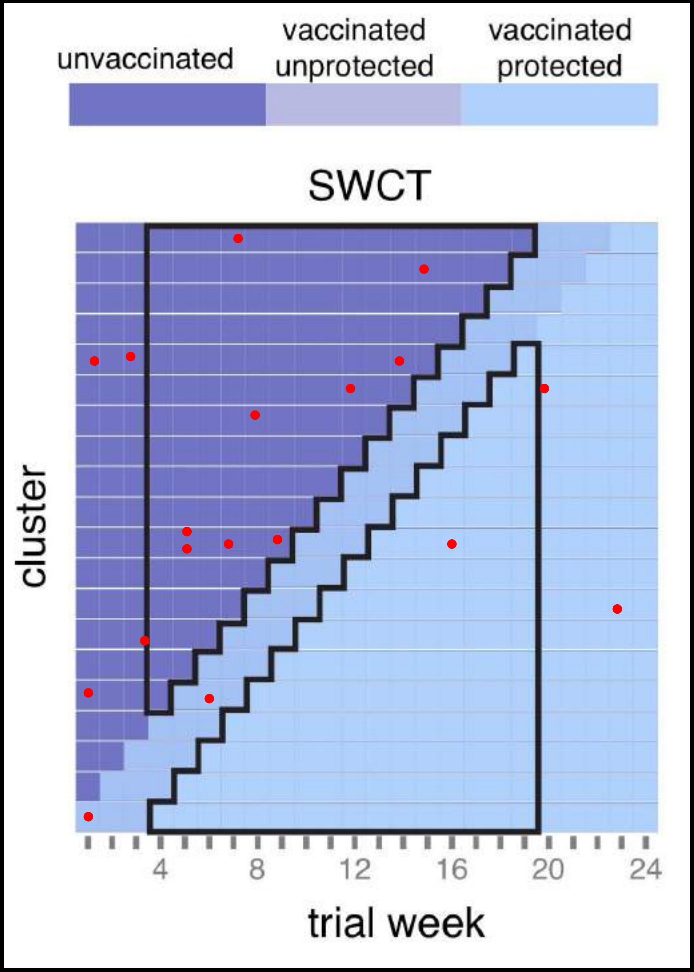
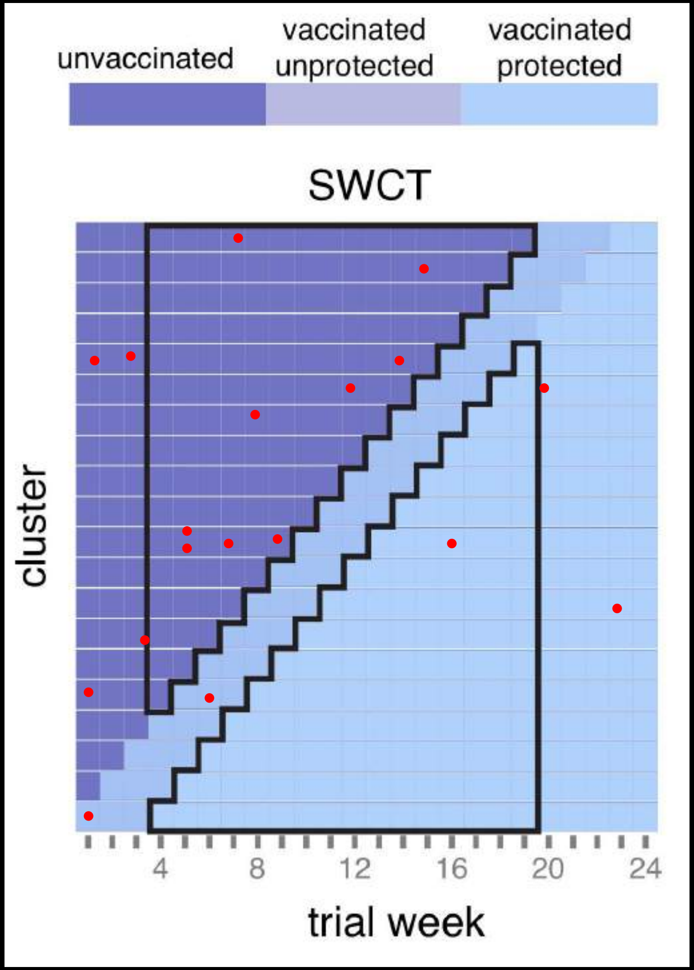


● infected participant

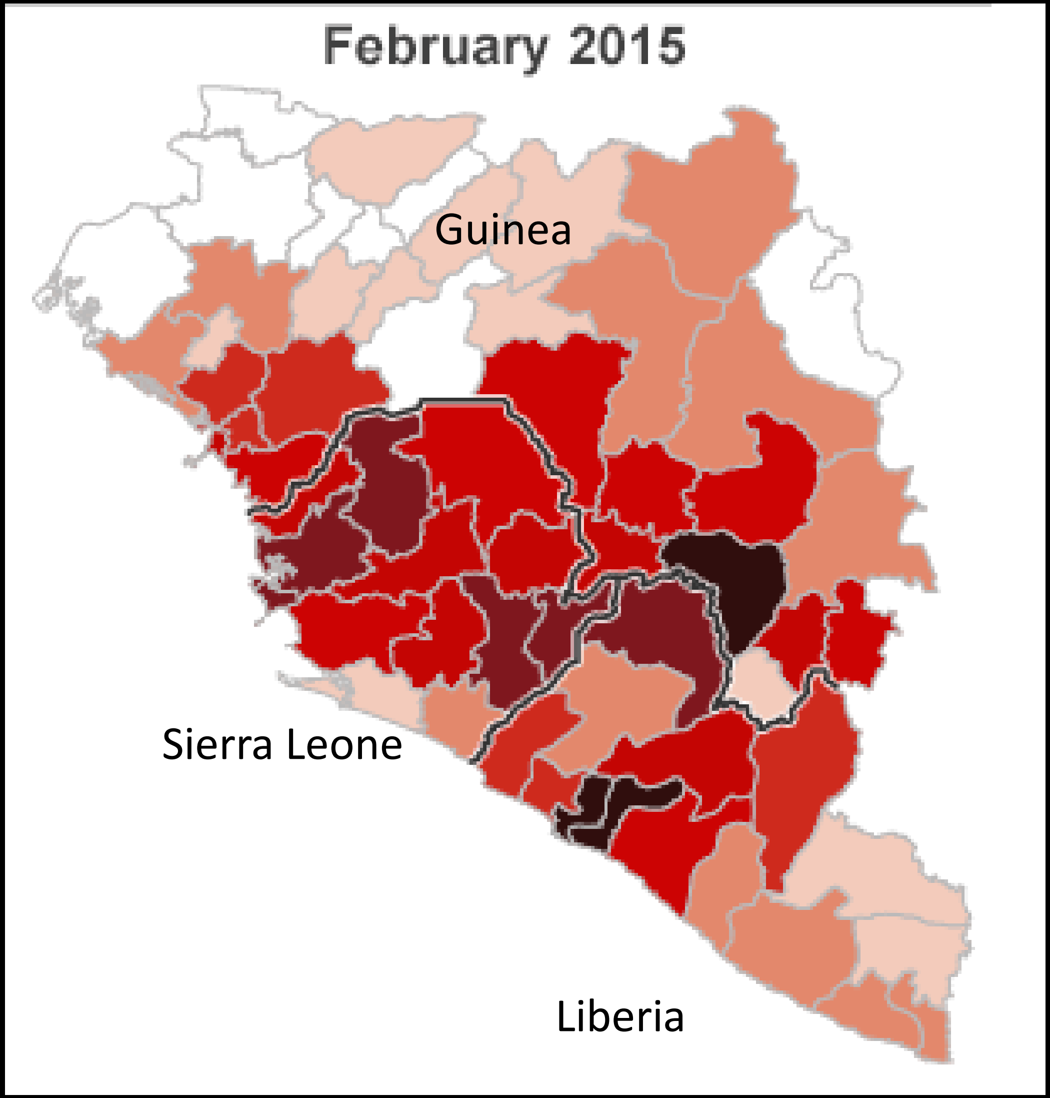
Stepped Wedge Cluster Trial



Nov 2014

Jan 2014

Regional Variation in Ebola Cases



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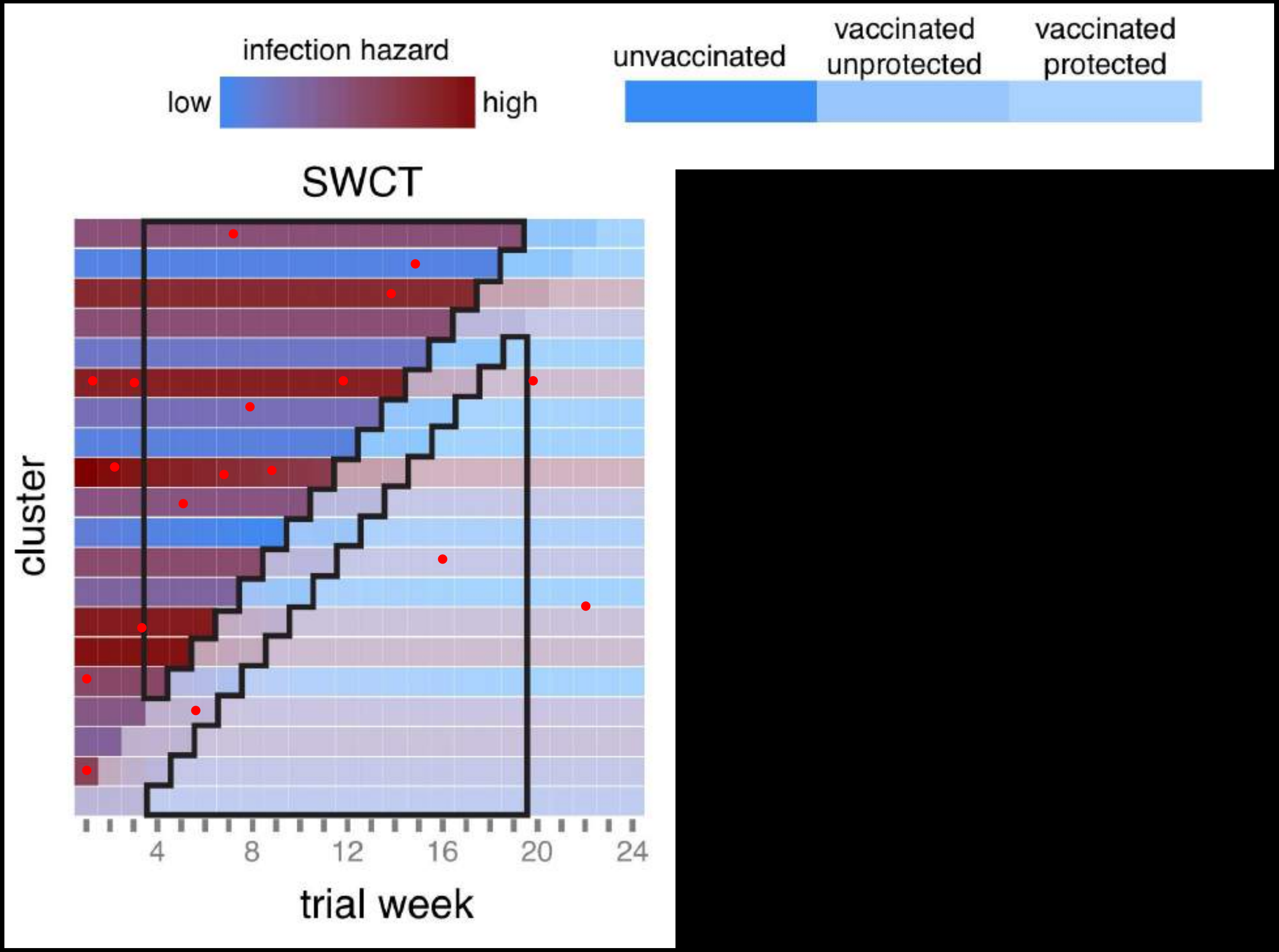

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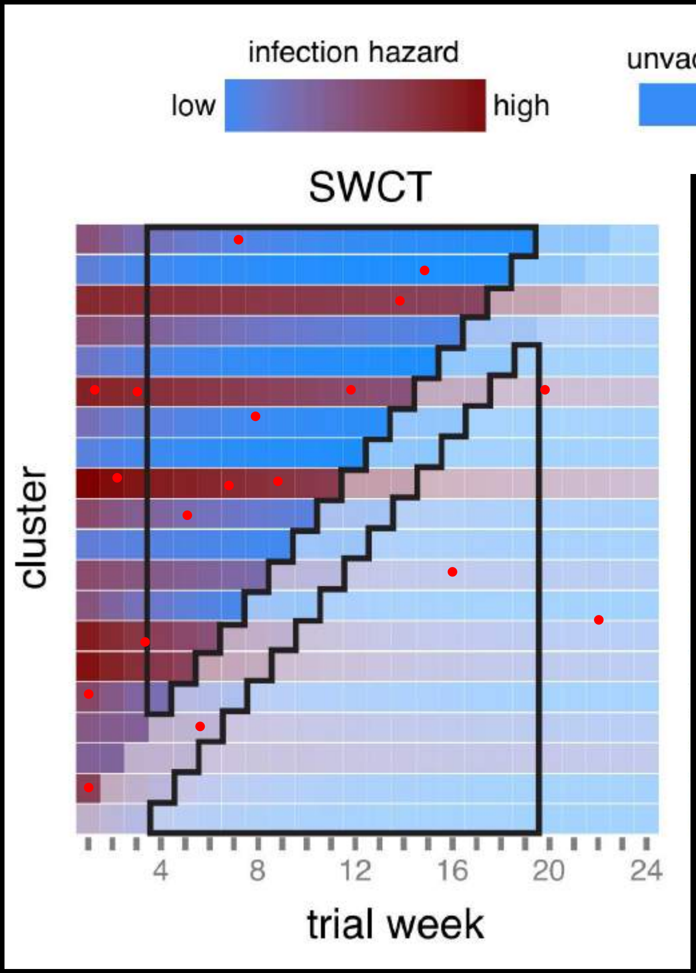

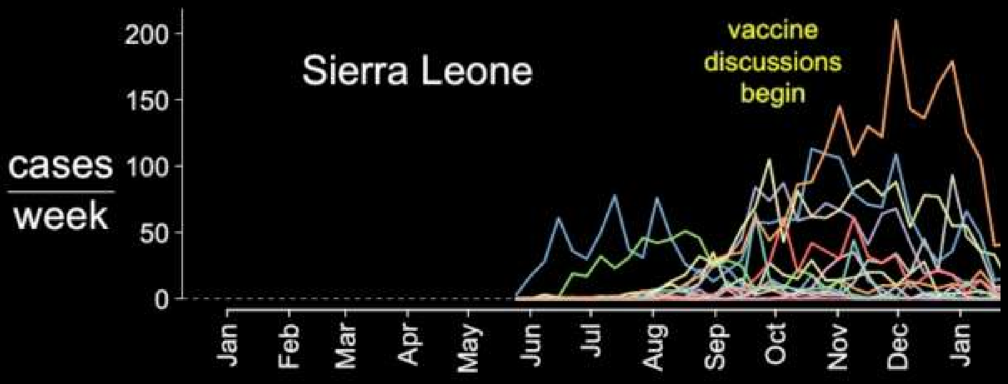

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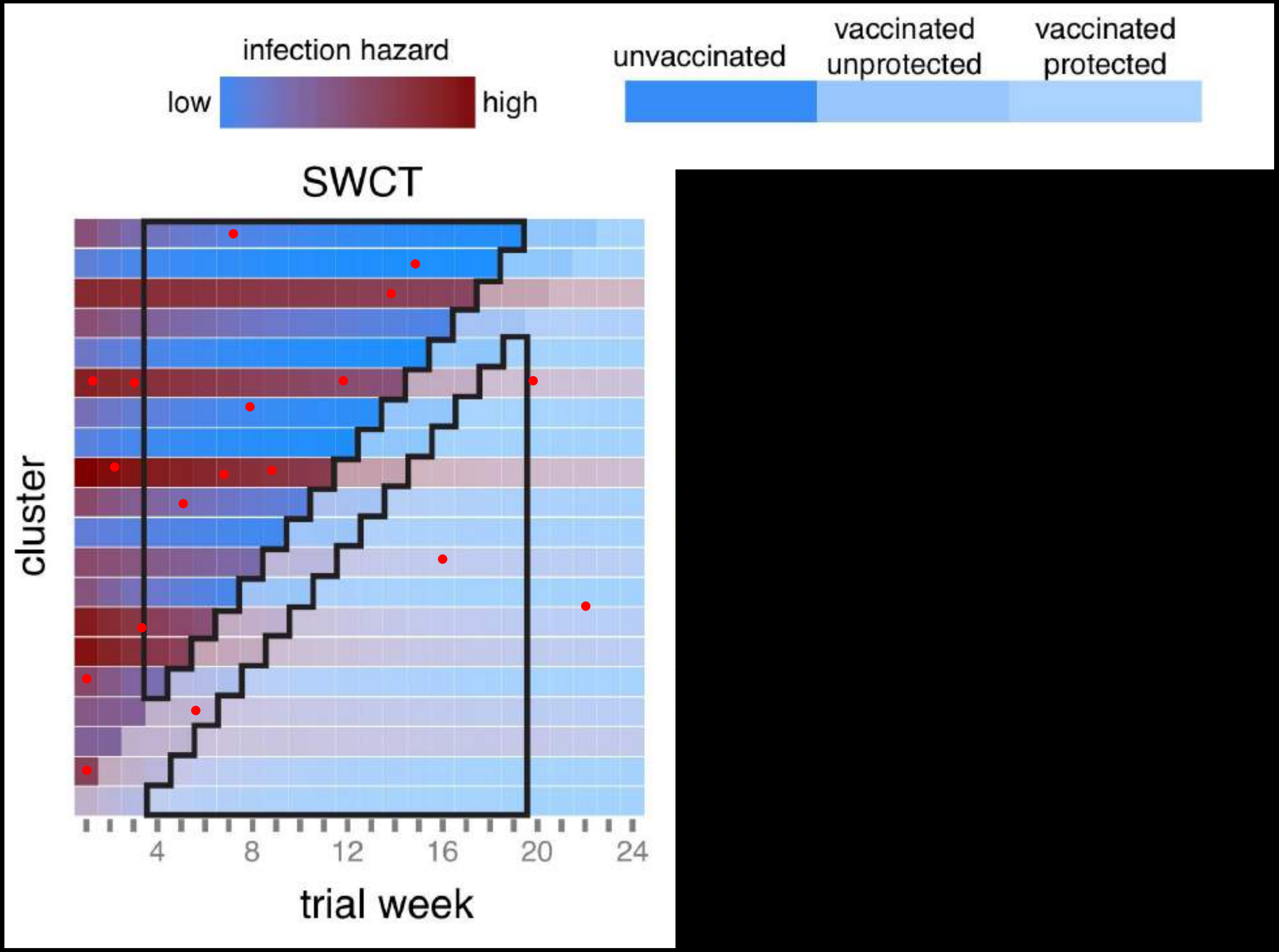
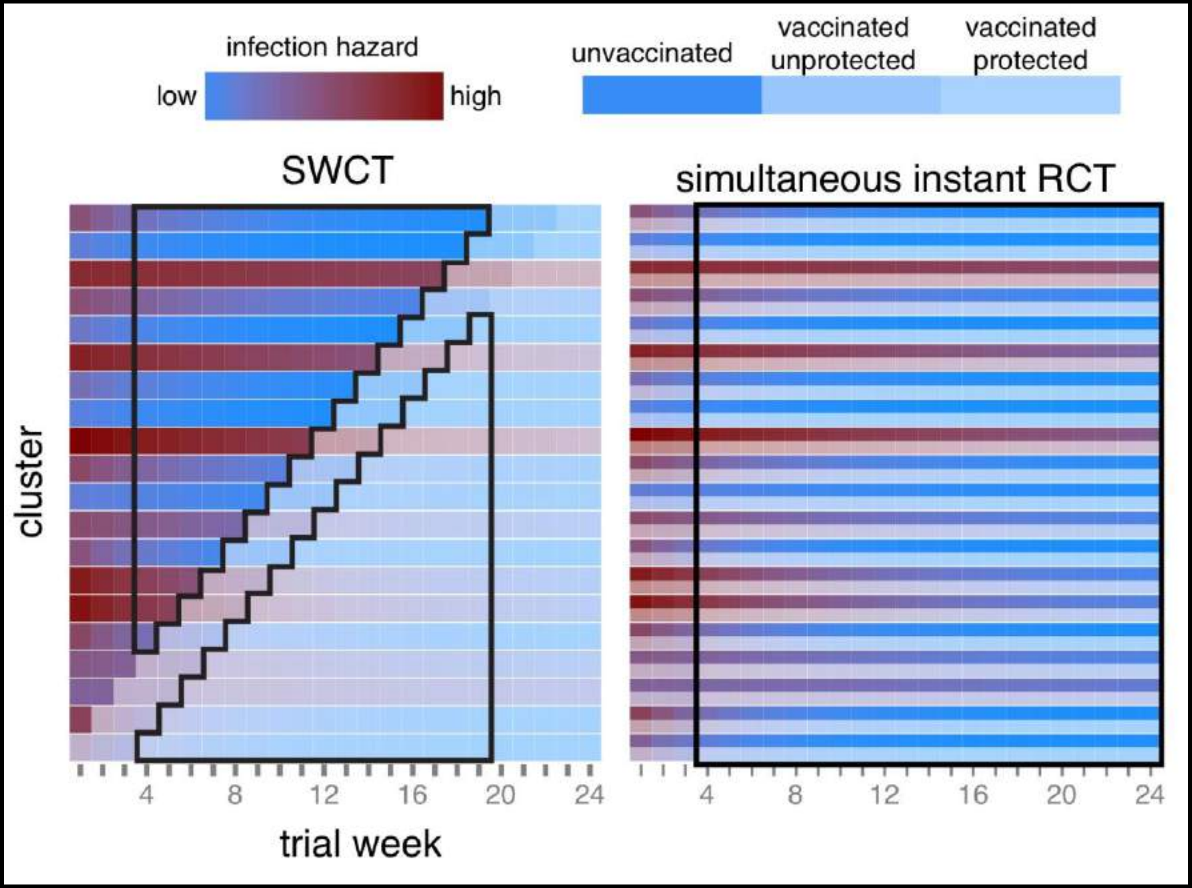


Other Options



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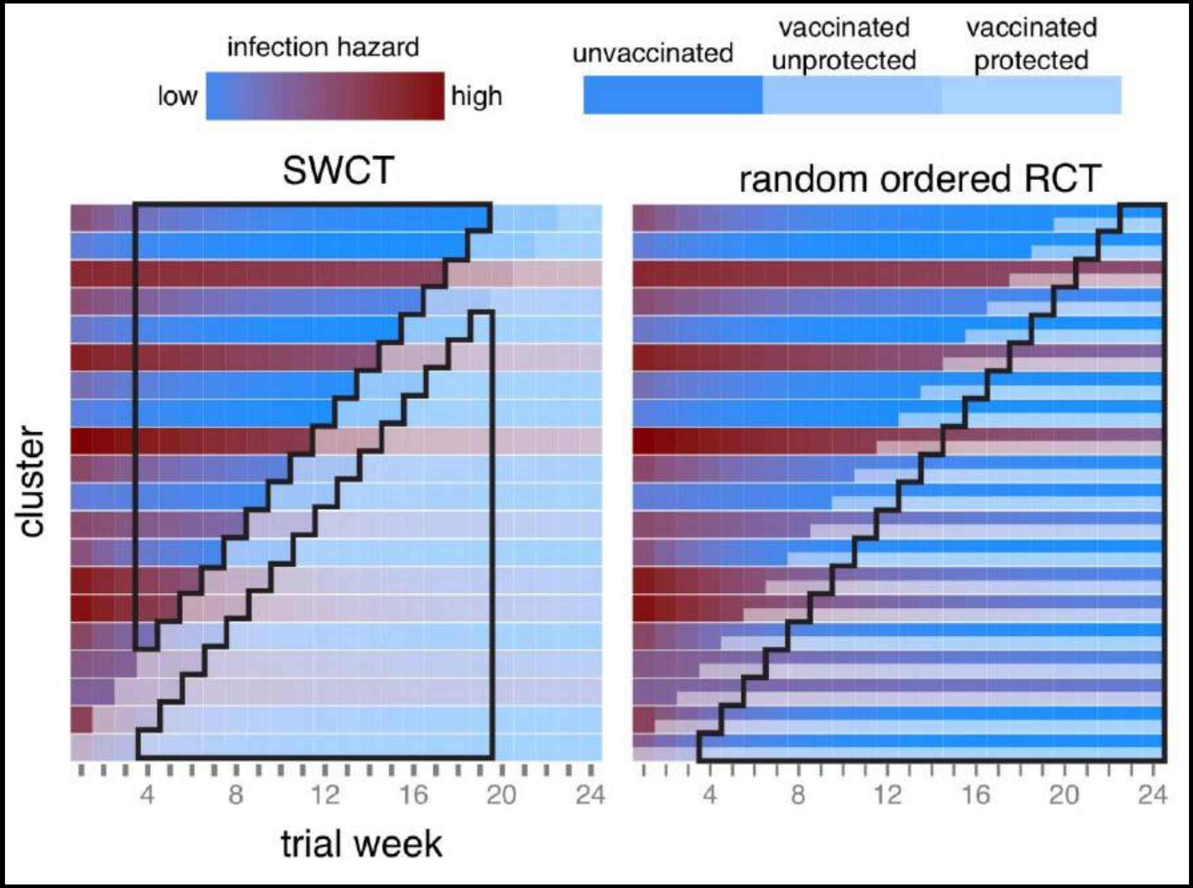

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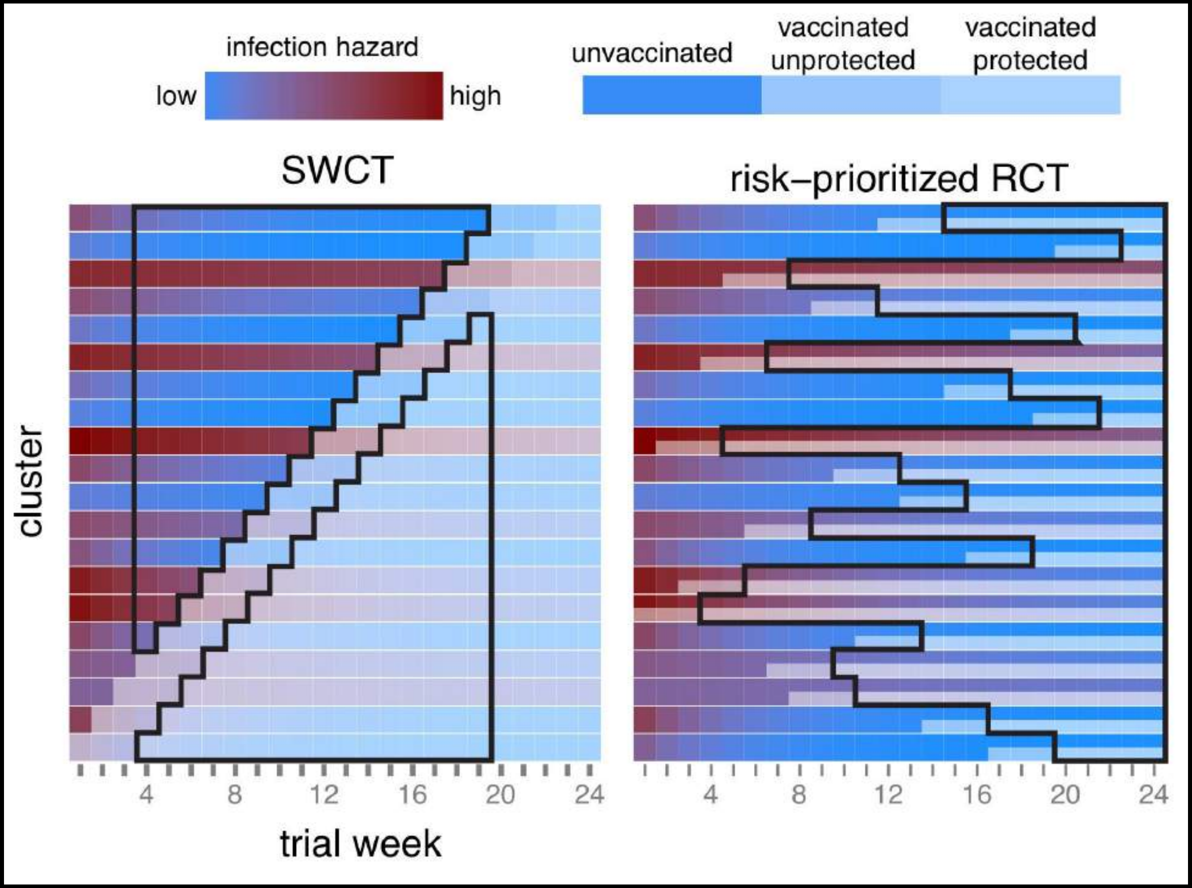
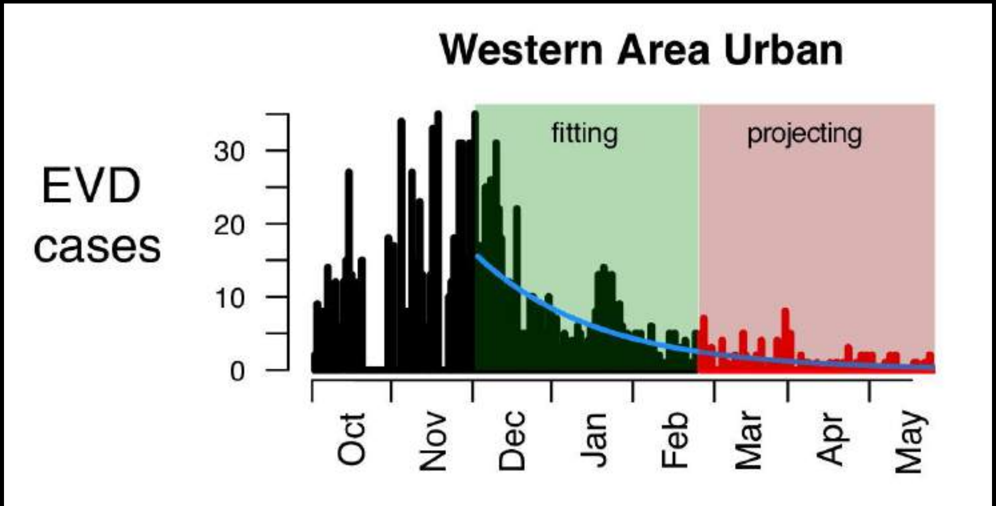


Project Declining Epidemics



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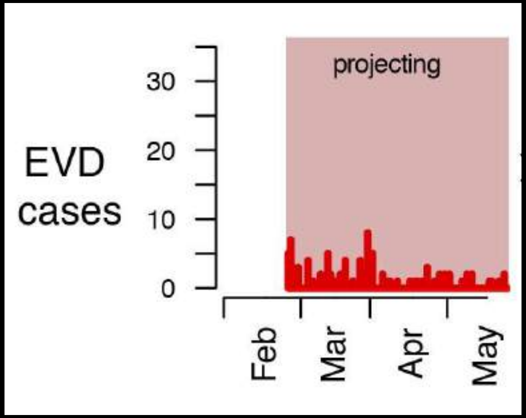

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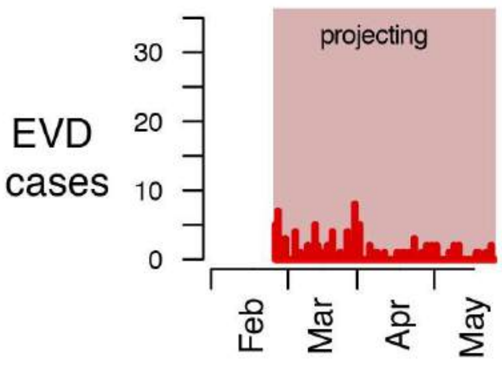
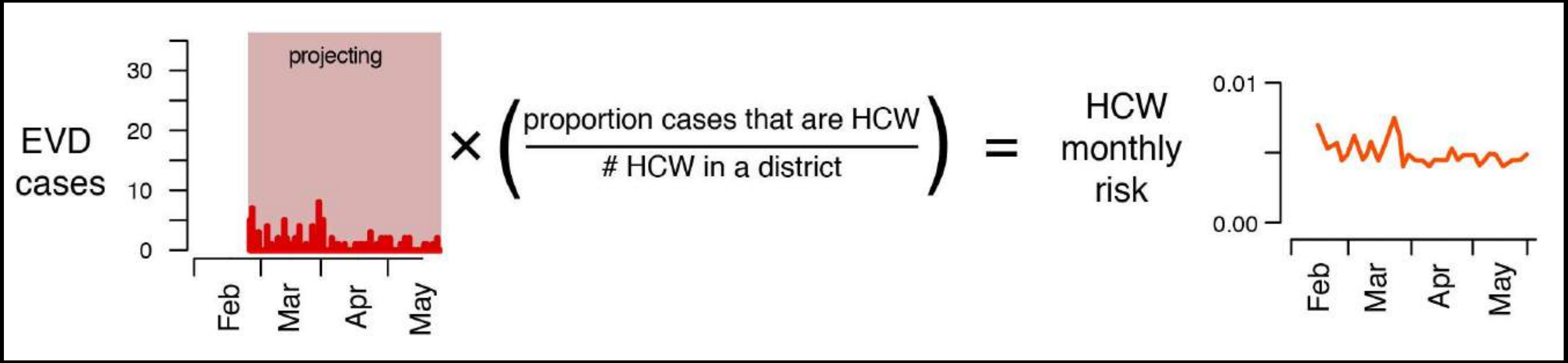
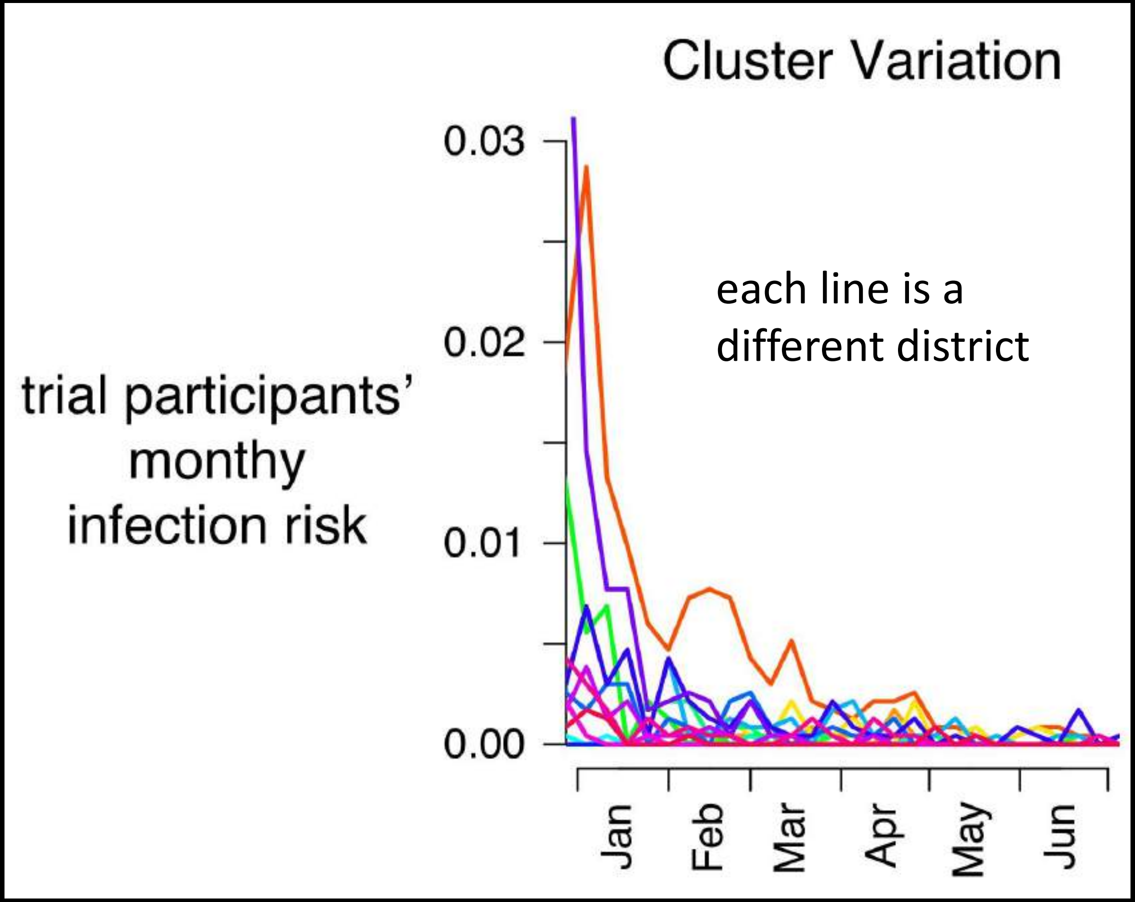


$$\times \left(\frac{\text{proportion cases that are HCW}}{\text{\# HCW in a district}} \right)$$

Project Declining Epidemics



Modeling Ebola Risk



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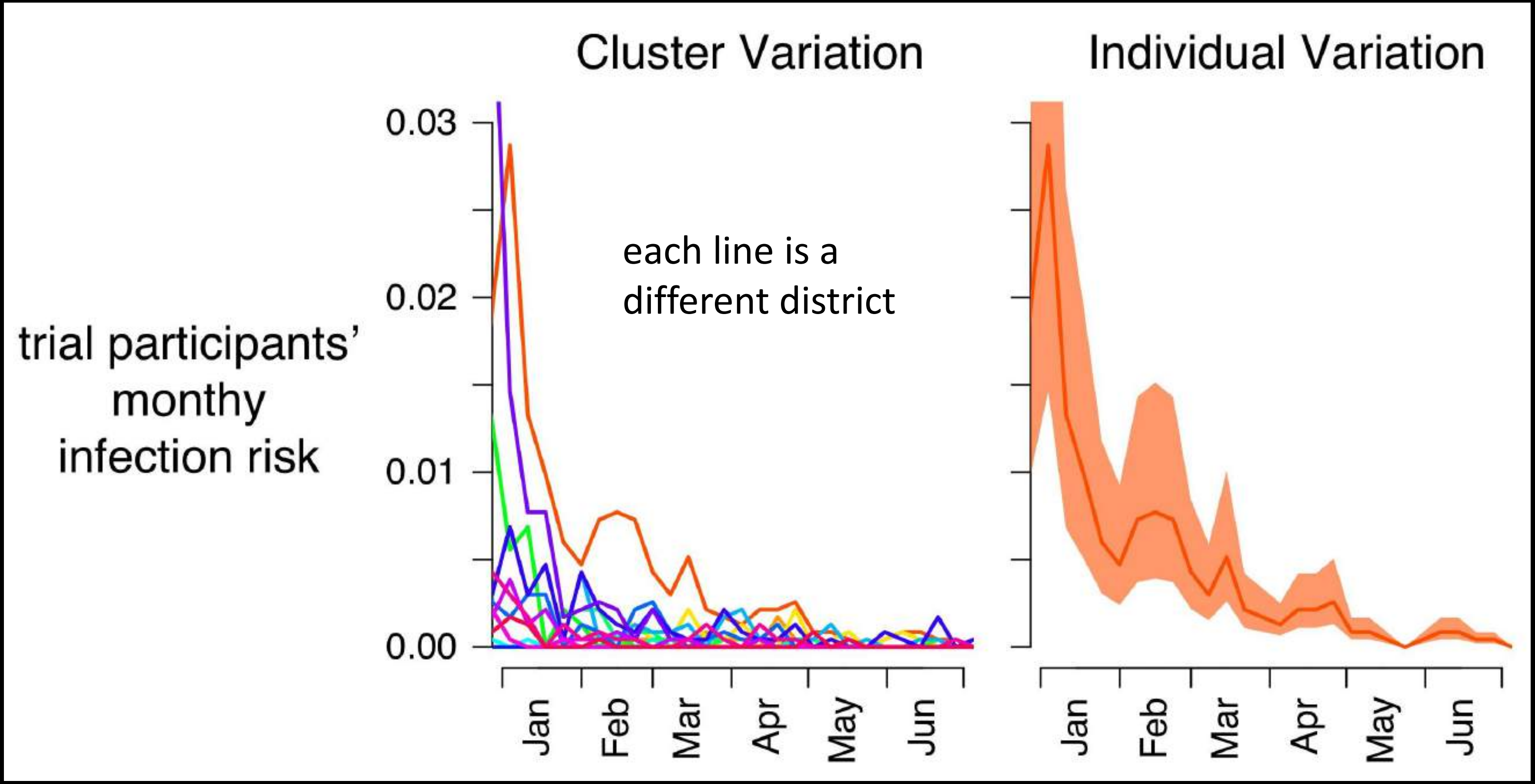


Evaluating Trial Designs

1. Fit epidemic declines with decay model.

1. Simulate stochastic epidemic projections
2. Simulate trial population with risk determined by projections.
3. Simulate vaccine trial design.
4. Analyze data.

× 2000 for each scenario

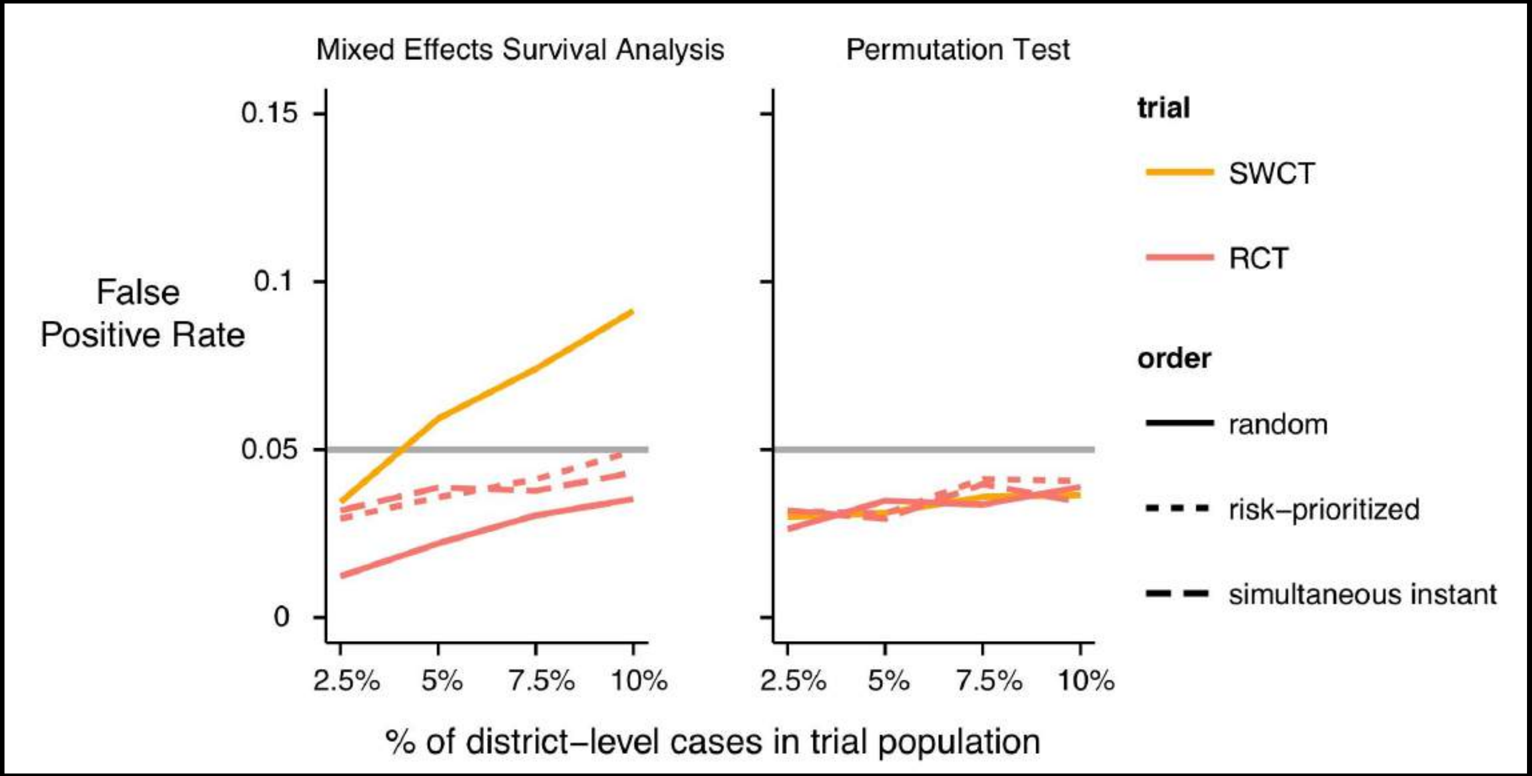
False Positive Rate

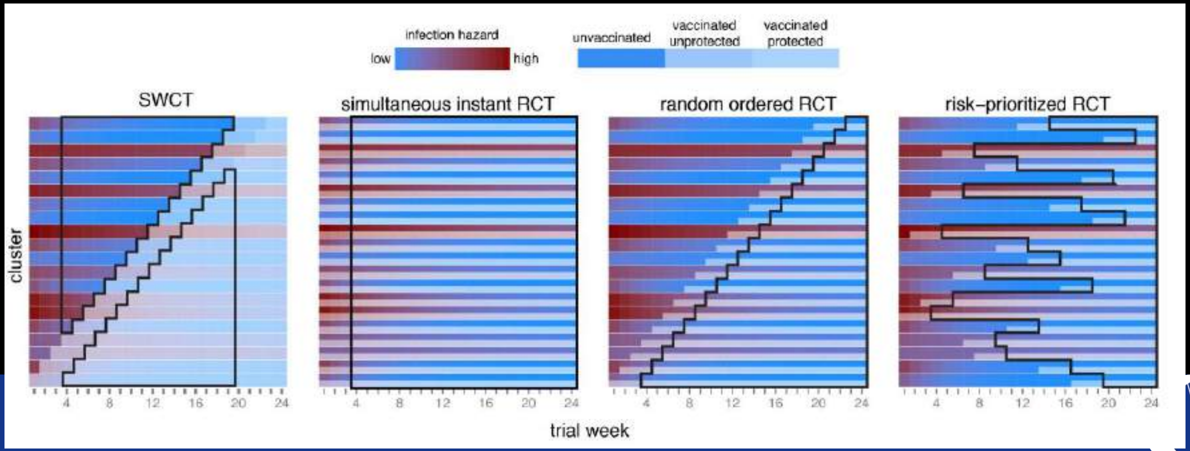
If vaccine is *not* efficacious, % times we conclude it is efficacious

Statistical Power

If vaccine is efficacious, % times we conclude it is efficacious

False Positive Rates





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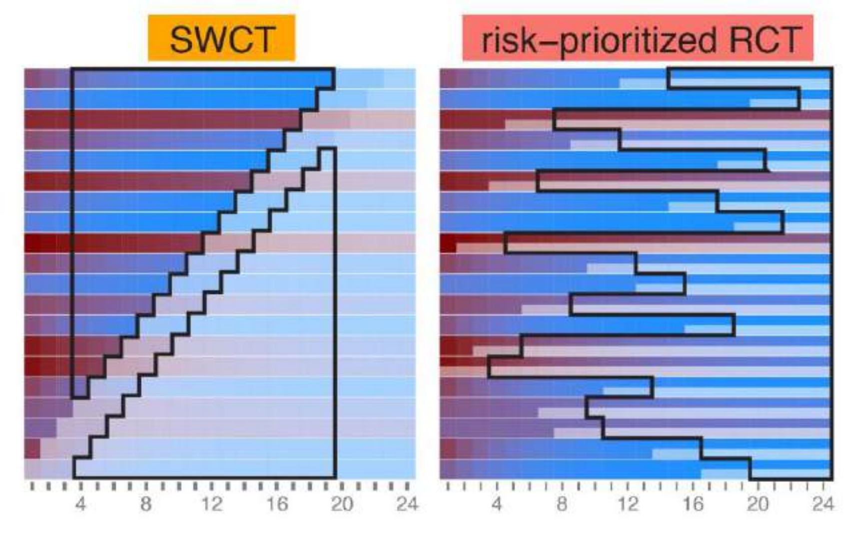
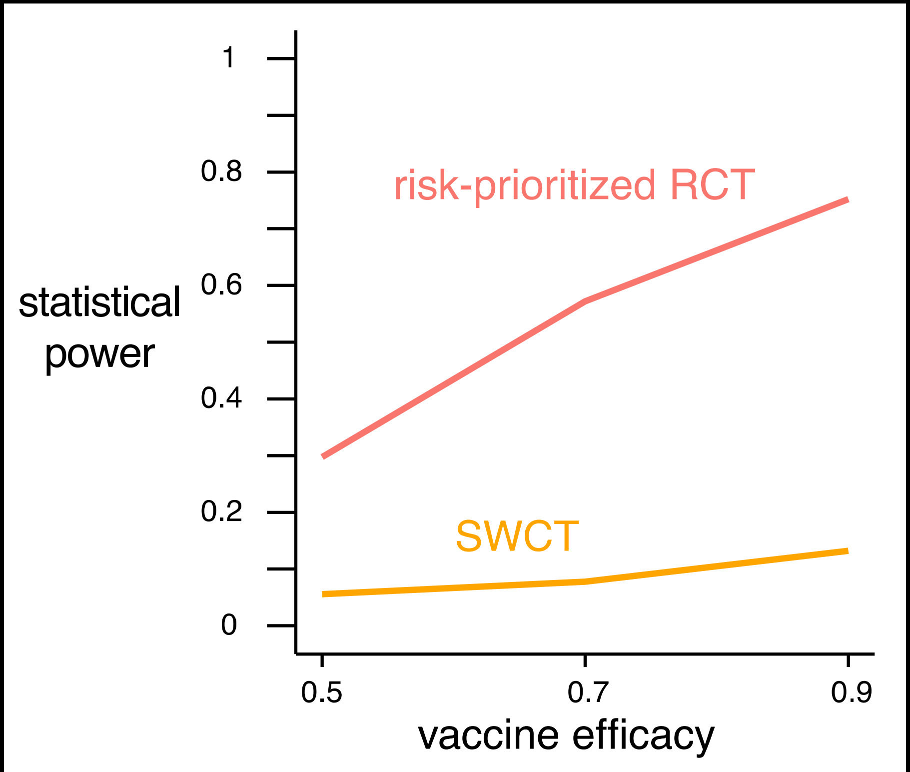
Statistical Power



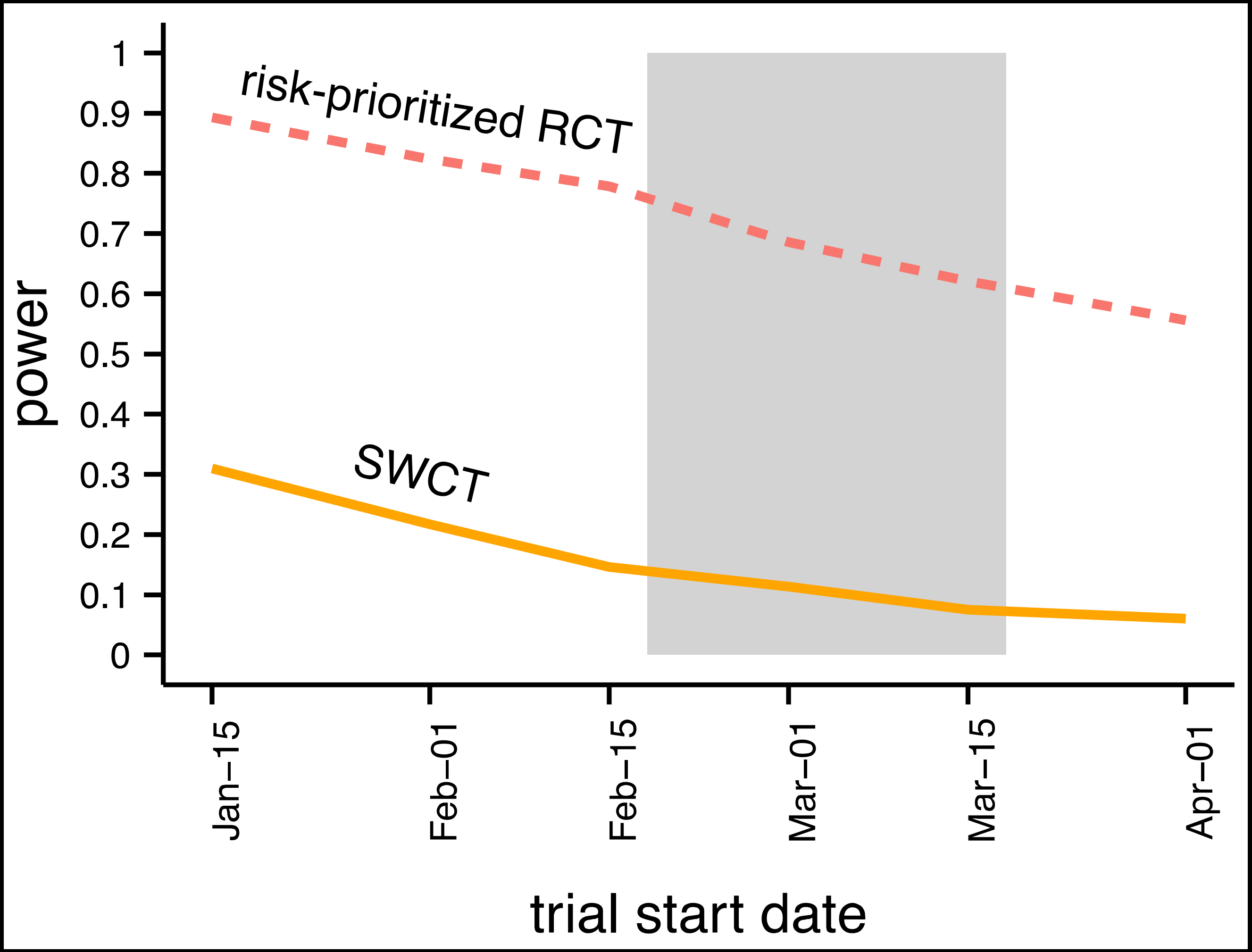
Risk-prioritized RCT far more statistically powerful in this context.



SWCT has < 15% power of detecting an efficacious vaccine.

Very inefficient for spatiotemporally variable settings

Speed is a Priority!



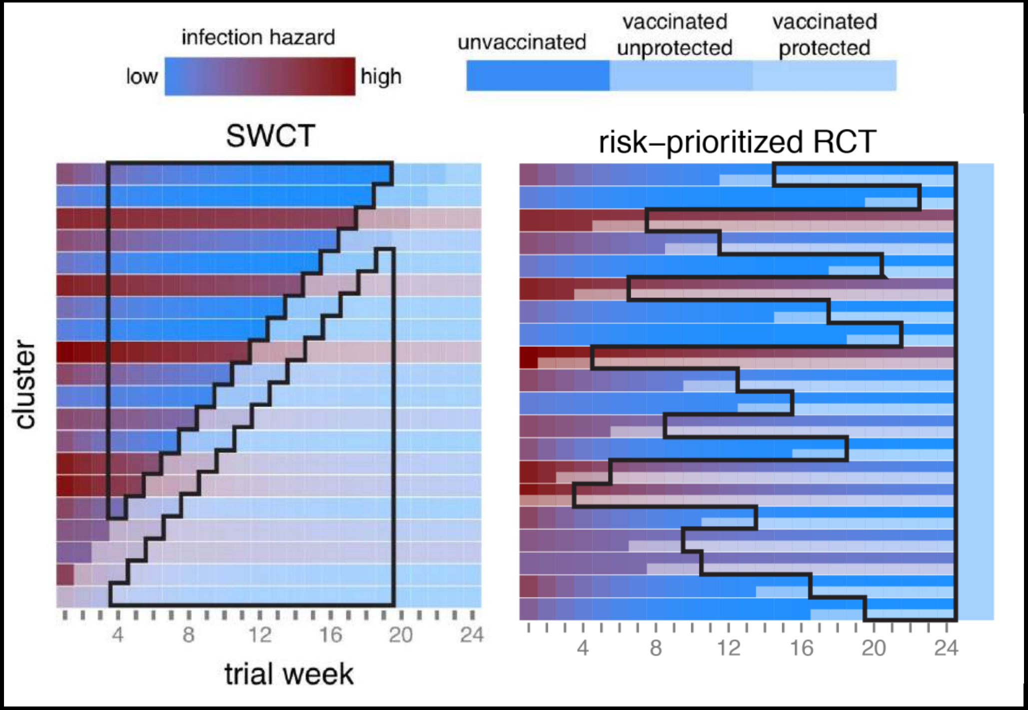
Bellan et al. 2015. *Lancet ID*.

What about ethics?

Avoids Equipoise Concern

1. No control groups
2. Vaccinate everyone *as fast as possible*

(no prioritization of information over outcomes)



But high risk people should be vaccinated first...

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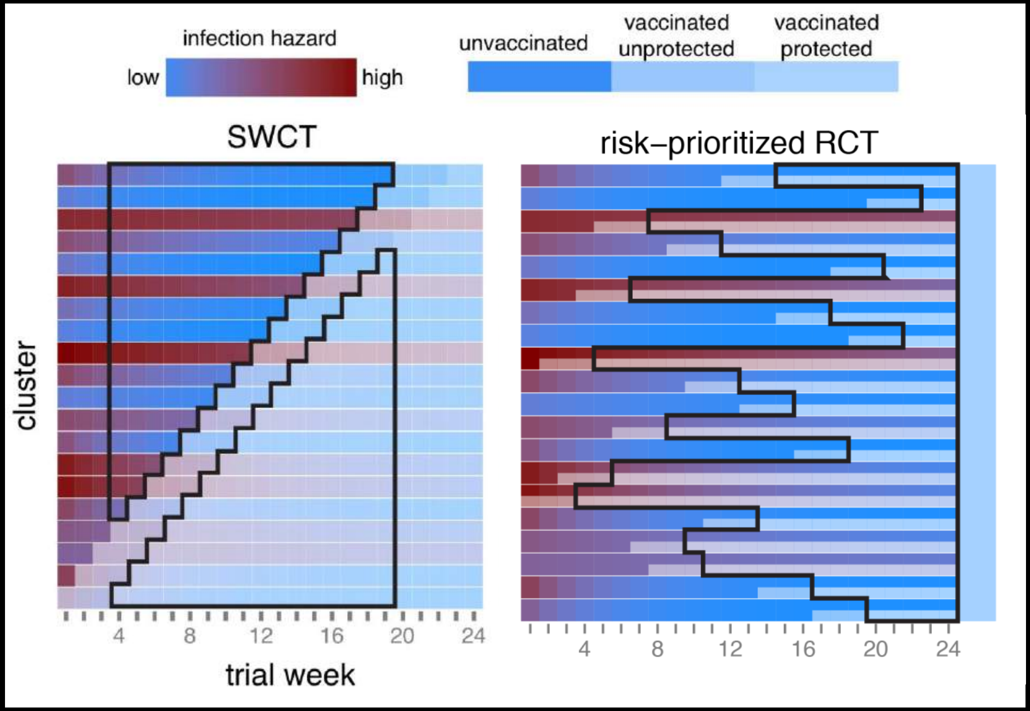

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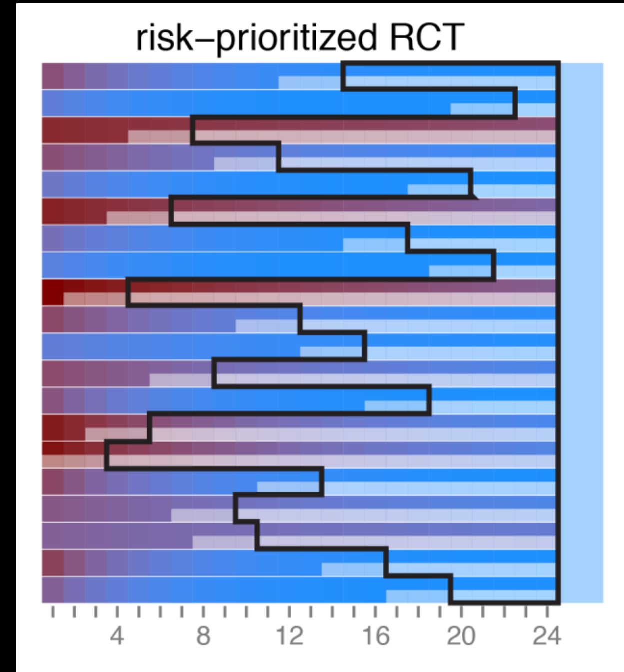
CDC

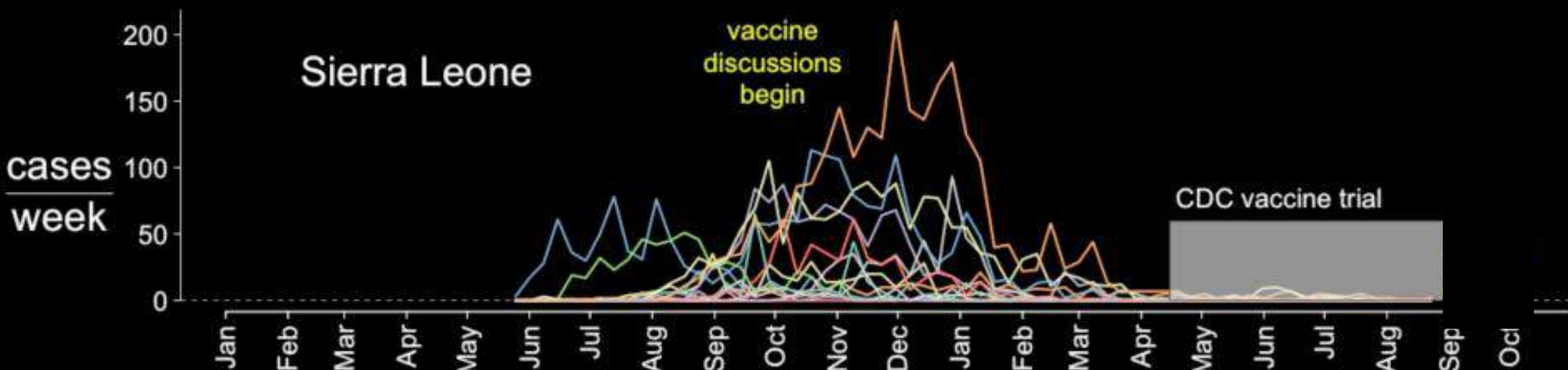
STRIVE

Sierra Leone Trial to Introduce a Vaccine against Ebola



Informed by our analysis,
CDC did a risk-prioritized RCT.

Vaccinated everyone at the end.



Computational Resources

- 600,000 simulated trials (2K for 300 scenarios)
- 480 million statistical models fit
- 2 days on TX Advanced Computing Cluster
- Total analysis done in 3 weeks

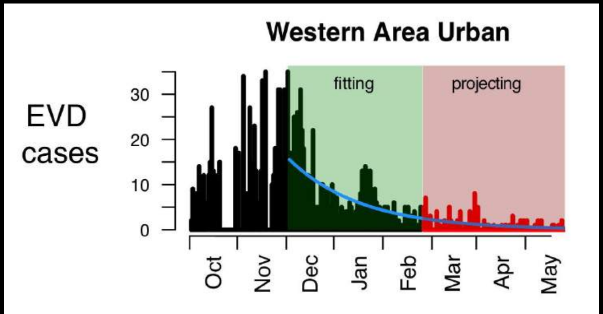
Interactions with CDC

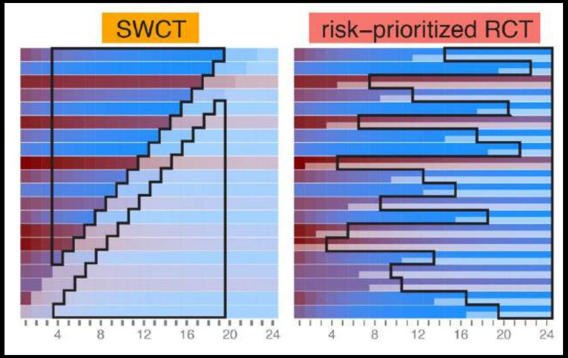
- Dialogue/collaboration with CDC Modelers (Lopman, Gambhir)
- Results discussed in CDC Vaccine Team Meetings
- CDC already leaning towards phased-RCT due to adaptability in declining epidemic context
- Results were influential in helping CDC think through new design
- Ongoing CDC STRIVE began April 14th

Integrative Approach

process-centric

data-centric





Model Taxonomy

CONTINUOUS TREATMENT OF INDIVIDUALS

(averages, proportions, or population densities)

DISCRETE TREATMENT OF INDIVIDUALS

DETERMINISTIC

CONTINUOUS TIME

DISCRETE TIME

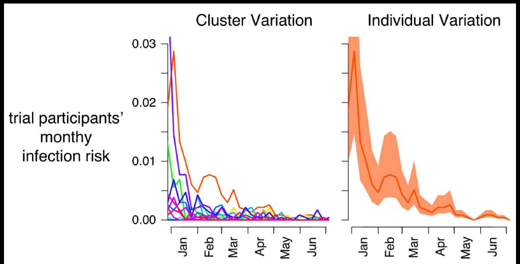
STOCHASTIC

CONTINUOUS TIME

DISCRETE TIME

CONTINUOUS TIME

DISCRETE TIME



ICI3D

Philosophy of Modeling & Trial Design

Analytical Power Analyses

Classical Power Simulations

Trials superimposed over transmission modeling

Risk-Model Fitted to Epi Data

Compartmental Models

Individual-Based Models

Abstract — Concrete

real world scenarios

Summary

- Trial design requires thinking both from data- & process- centric perspectives

- Simulation can reveal weaknesses in designs

- Intuitive arguments for specific designs may be wrong ➔ SIMULATE!

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FOGARTY

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SACEMA
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